

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

ATTORNEY'S DOCKET NUMBER
9052-111
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

10/088245

INTERNATIONAL APPLICATION NO.
PCT/GB00/03568

INTERNATIONAL FILING DATE
18 September 2000

PRIORITY DATE CLAIMED
17 September 1999

TITLE OF INVENTION

TARGET FOR ANTIVIRAL THERAPY

APPLICANT(S) FOR DO/EO/US

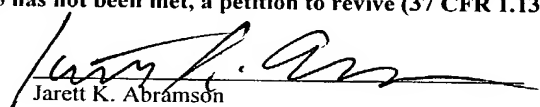

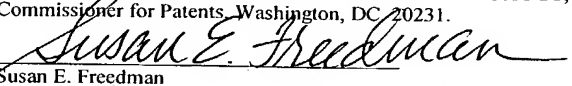
ANTSON, Alfred; MAITLAND, Norman

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau):
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☐ Amendments to the claims of the International Application Under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report Under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☒ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
20. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.51)		INTERNATIONAL APPLICATION NO. PCT/GB00/03568		ATTORNEY DOCKET NO 9052-111	
21. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a) (1) - (5)):				CALCULATIONS PTO USE ONLY	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....				\$1040.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....				\$890.00	
International preliminary examination fee 37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....				\$740.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4).....				\$710.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4).....				\$100.00	
ENTER APPROPRIATE BASE FEE AMOUNT =				\$890.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	40 - 20 =	20	x \$18.00	\$360.00	
Independent Claims	15 - 3 =	12	x \$84.00	\$924.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$280.00	\$1008.00	
TOTAL OF ABOVE CALCULATIONS =				\$	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2				\$	
SUBTOTAL =				\$	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$	
Fee for Recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
TOTAL FEES ENCLOSED =				\$2240.00	
				Amount to be refunded:	\$
				charged:	\$18.00
<p>a. <input checked="" type="checkbox"/> A check in the amount of \$2240.00 to cover the above fees is enclosed.</p> <p>b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 50-0220 in the amount of \$18.00 to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0220. A duplicate copy of this sheet is enclosed.</p> <p>d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.</p>					
<p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO:</p>					
<p style="text-align: right;">  Jarett K. Abramson </p> <p style="text-align: right;">Date: March 15, 2002</p>					
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;">  20792 PATENT TRADEMARK OFFICE </div> <div style="width: 50%;"> <p style="text-align: center;">CERTIFICATE OF EXPRESS MAILING</p> <p>Express Mail Label No. EL 920740629 US</p> <p>Date of Deposit: March 15, 2002</p> <p>I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX PCT, Attn: DO/EO/US, Commissioner for Patents, Washington, DC 20231.</p> <p style="text-align: right;">  Susan E. Freedman </p> </div> </div>					

Attorney's Docket No. 9052-111

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Antson et al.	Examiner:	To be assigned
Serial No.:	PCT/GB00/03568	Group Art Unit:	To be assigned
Filed:	September 18, 2000		
For:	Target for Antiviral Therapy		

Date: March 15, 2002

Box PCT
U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202
Attn: DO/EO/US

PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above application, please amend the above referenced application as follows. Please enter the following amendments prior to the calculation of the filing fee. Pursuant to the rules for amendments under 37 C.F.R. §1.121, the claims have been amended herein using the rewritten claims format. The present amendment also includes a section entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**" attached hereto.

IN THE SPECIFICATION:

Please amend the specification as follows:

On page 1 after the title of the invention please add:

RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 371 from PCT/GB00/03568, (published under PCT Article 21(2) in English), filed on September 18, 2000, which claims priority to Great Britain Application Serial No. 9921938.8, filed on September 17, 1999, the disclosures of which are incorporated by reference herein in their entireties.

IN THE CLAIMS:

Please enter the amended claims as follows:

2. (Amended) The E2NT dimer protein of Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.
3. (Amended) The E2NT dimer protein of Claim 1, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.
4. (Amended) The E2NT dimer protein of Claim 3 comprising three clusters.
5. (Amended) The E2NT dimer protein of Claim 3 wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues: Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.
6. (Amended) The E2NT dimer protein of Claim 3, wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.
7. (Amended) The E2NT dimer protein of Claim 3, wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues: Pro106, Lys111, Phe168, Trp134.
8. (Amended) The E2NT dimer protein of Claim 1, further comprising residues associated with transactivation and/or replication properties of E2.
9. (Amended) The E2NT dimer of Claim 8, wherein the residues comprise any one or more of the following residues: Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

10. (Amended) A method for determining the structure of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, wherein the E2NT dimer protein and any of its mutations are mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. (Amended) The method according to Claim 10 in rationalised antiviral drug design.

12. (Amended) A method for identifying and/or selecting a candidate therapeutic agent, the method comprising:

determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2 *in vitro*.

13. (Amended) The method according to Claim 12 further comprising identifying and/or selecting an antiviral candidate therapeutic agent.

14. (Amended) The method according to Claim 13, wherein the identifying and/or selecting of the antiviral candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. (Amended) A method of treating an HPV infection in a subject comprising:
introducing an E2NT dimerisation inhibitor in said subject.

16. (Amended) The method according to Claim 15 further comprising treating warts, proliferative skin lesions and/or cervical cancer.

18. (Amended) Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to

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Please cancel claim 33 without prejudice or disclaimer.

Please add the following new claims:

34. (New) A method for designing a potential antiviral compound for the prevention or treatment of an HPV infection, comprising:

a) obtaining crystals of the E2NT dimer protein such that the three dimensional structure of the crystallized E2NT dimer protein can be determined to a resolution of about 1.9 Å or better,

b) evaluating the three dimensional structure of the crystallized E2NT dimer protein;

c) synthesizing the potential antiviral compound based on the three-dimensional crystal structure of the crystallized E2NT dimer protein;

d) contacting an HPV virus with the potential antiviral compound; and

e) assaying the HPV virus for infectivity or monitoring the virus for activity, or both, whereby a decrease in the infectivity of the virus or a change in the activity of the virus indicates the compound may be used for the prevention or treatment of an HPV infection.

35. (New) The method according to claim 34, wherein the antiviral compound is a peptide or polypeptide.

36. (New) The method according to claim 34, wherein the E2 N-terminal module dimer protein or homologue thereof comprises residues vital for transcriptional and replication activities of said protein.

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37. (New) The method according to claim 36, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

38. (New) The method according to claim 37, wherein said E2NT dimer protein comprises three clusters.

39. (New) A method for designing a candidate compound for screening for binding to or inhibition of an HPV infection, comprising:

a) utilizing the three dimensional structure of a crystallized E2NT module dimer protein wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer; and

b) designing a candidate binding compound based on the three-dimensional crystal structure of the crystallized E2NT dimer protein for binding to said dimer protein.

40. (New) The method of claim 39, wherein the candidate compound is a peptide or polypeptide.

41. (New) A method for determining the crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, wherein the E2NT dimer protein and any of its mutations is mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

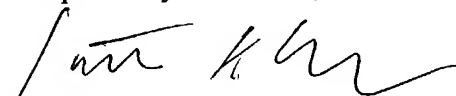
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REMARKS

Please note that the claims pending at the time of this filing are the claims of the international application serial no. PCT/GB00/03568, *i.e.* claims 1-33. Claim 33 has been cancelled and claims 34-41 have been added. The pending claims have been amended above to better conform to United States practice. The marked-up version of the changes to the specification and claims are attached hereto in the "Version With Markings to Show Changes Made".

It is respectfully submitted that this application is now in condition for substantive examination, which action is respectfully requested.

Respectfully submitted,



Jarett K. Abramson
Attorney for Applicants
Registration No. 47,376

Enc: Version With Markings to Show Changes Made

CUSTOMER NO.



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Date of Deposit: March 15, 2002

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Susan E. Freedman

Date of Signature: March 15, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

2. (Amended) [An] The E2NT dimer protein [according to] of Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.
3. (Amended) [An] The E2NT dimer protein [according to either preceding claim] of Claim 1, wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.
4. (Amended) [An] The E2NT dimer protein [according to] of Claim 3 comprising three clusters.
5. (Amended) [An] The E2NT dimer protein [according to either of Claims] of Claim 3 [or 4] wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues: Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.
6. (Amended) [An] The E2NT dimer protein [according to any one of Claims 3-5] of Claim 3, wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.
7. (Amended) [An] The E2NT dimer protein [according to any one of Claims 3-6] of Claim 3, wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues: Pro106, Lys111, Phe168, Trp134.
8. (Amended) [An] The E2NT dimer protein [according to any preceding claim] of Claim 1, further comprising residues associated with transactivation and/or replication properties of E2.

9. (Amended) [An] The E2NT dimer [according to] of Claim 8, wherein the residues comprise any one or more of the following residues: Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.
10. (Amended) [Use of a] A method for determining the structure of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, [according to any preceding claim or homologue thereof in mapping mutations] wherein the E2NT dimer protein and any of its mutations are mapped onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.
11. (Amended) [Use] The method according to Claim 10 in rationalised antiviral drug design.
12. (Amended) [An *in vitro*] A method for identifying and/or selecting a candidate therapeutic agent, the method comprising:
determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2 *in vitro*.
13. (Amended) [Use of the] The method according to Claim 12 [in] further comprising identifying and/or selecting an antiviral candidate therapeutic agent.
14. (Amended) [Use according to] The method according to Claim 13, wherein [identification/selection] the identifying and/or selecting of the antiviral candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.
15. (Amended) [Use of an E2NT dimerisation inhibitor for the preparation of a medicament for treatment of conditions that arise as a result of] A method of treating an HPV infection in a subject comprising:

introducing an E2NT dimerisation inhibitor in said subject.

16. (Amended) [Use] The method according to Claim 15 [for the treatment of] further comprising treating warts, proliferative skin lesions and/or cervical cancer.

18. (Amended) Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to [any one of Claims 1-9] Claim 1 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

20. (Amended) [A] The method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

21. (Amended) [A] The method of claim 19, [or claim 20] wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

22. (Amended) [A] The method of [any of claims] Claim 19 [to 21], wherein the crystal structure comprises the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.

23. (Amended) [A] The method of [any of claims] Claim 19 [to 22], wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

32. (Amended) A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex [according to claim 27 or claim 28] comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3 or a homologue of said molecule or

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molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

- a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and
- b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

Claim 33 has been canceled without prejudice or disclaimer.

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Target for Antiviral Therapy

The present invention provides a crystallised module of a nuclear phosphoprotein and an assay and method for determining interactions with human papillomavirus E2 for use in drug design, for use particularly but not exclusively in designing antiviral agents with potential use in treating warts, proliferative skin lesions and carcinoma of the cervix.

Background to the Invention

10

Human papillomaviruses (HPVs) cause warts and proliferative lesions in skin and other epithelia. In a minority of HPV types ("high risk", which include HPVs 16, 18, 31, 33, 45 and 56), further transformation of the wart lesions can produce tumours, most notably carcinoma of the cervix¹. HPVs have evolved a sophisticated system of control, mediated by protein:DNA and protein:protein interactions, that involves both cellular and viral proteins. The 45 kDalton nuclear phosphoprotein, E2, has two central roles in this control. It acts as the principal virally encoded transcription factor and, in association with the viral E1 protein, it creates the molecular complex at the origin of the viral DNA replication².

20

E2 has three distinct modules. The N-terminal module (E2NT) of about 200 amino acids is responsible for interactions with viral and host cell transcription factors. It is followed by a flexible, proline-rich, linker module and a C-terminal module (E2CT), each of about 100 amino acids³ (Fig. 1a). The E2CT binds as a homodimer to DNA sites with a consensus sequence of ACCGN₄CGGT⁴. In most HPVs a long upstream regulatory region (URR) precedes the viral genes and contains four spatially conserved E2 binding sites: three sites proximal to the transcription start site (p97 in HPV16) and one approximately 500bp upstream.

30

The dimer of E2CT serves to anchor E2 protein to its recognition sites on the DNA, the function of the E2NT is to bind and localise at least three cellular transcription

factors, Sp1, TFIIB and AMF-1, to the transcription initiation complex. In addition, E2 interacts with another viral protein, E1, which has ATPase and helicase activities. E1 itself binds to the viral origin of replication which consists of about 100 bp and is surrounded by the three E2-binding sites, proximal to the transcription start. The
5 E2:E1 interaction greatly increases the rate of HPV genome replication^{2,5,6}, Fig. 1a. An intact E2 is essential for the normal productive (wart) life cycle of HPV, however during malignant progression HPV DNA is integrated into the host cell genome, which usually results in disruption of the E2/E1 ORFs and loss of E2 protein, in turn leading to dysregulated expression of the viral oncogenes E6 and E7⁷.

10

Consistent with its role as a transcription regulator, E2 has been shown to direct the formation of loops in DNA containing E2 binding sites⁸. The loops were only formed with intact E2, and not with the E2CT alone. The E2 binding sites did not function independently and their co-operative effect was mediated by full length E2,
15 leading the authors to suggest that there were specific interactions mediated by E2 that bridged across the set of DNA binding sites through its N-terminal. A similar DNA loop structure could also be achieved with Sp1, a cellular transcription factor, which forms a complex with distally bound E2⁹; Sp1/E2 interactions are critical for transcription activation in BPV¹⁰.

20

Eighty six known E2 proteins from different species and different human subtypes¹¹ are highly conserved, with sequence identities typically of 35% in the N and C-terminal modules (Fig. 1b). The crystal structure of the E2CT has been determined both alone and in complex with cognate DNA¹²⁻¹⁴. The module is a dimer with a
25 barrel fold, and induces substantial bending (42-44°) of the DNA from its B-form double helix¹⁴.

The structure of the proteolytic fragment of HPV18 E2NT, missing 65 N-terminal residues, was recently reported at 2.1 Å spacing¹⁵. This allowed some analysis of
30 mutational effects on function, although the missing 65 amino acids contain residues which are essential for the transcriptional and replication activities of the protein.

We report herein the structure of the complete E2NT determined by X-ray analysis at 1.9 Å. We have found that it is an L-shaped molecule with the residues vital for transcriptional and replication activities of the protein lying on opposite sides of the N-terminal domain. Surprisingly, our results show that the surface, vital for transcription activation, is in fact involved in association of two E2NT's into a dimer. We suggest that dimerisation of E2NT plays an important and key role in induction of DNA loop formation, the mechanism by which distally bound transcription factors would be brought close to the site of transcription initiation. More importantly, our results raise the possibility that dimer formation serves as a molecular switch between early gene expression and viral genome replication during HPV infection.

The process of rationalised drug design requires no explanation or teaching for the skilled person but a brief description is given here of computational design for the lay reader: various computational analyses are necessary to determine whether a molecule is sufficiently similar to the target moiety or structure. Such analyses may be carried out in current software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., Waltham, Mass.) version 3.3, and as described in the accompanying User's Guide, Volume 3 pages. 134-135.

The Molecular Similarity application permits comparisons between different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: 1) load the structures to be compared; 2) define the atom equivalences in these structures; 3) perform a fitting operation; and 4) analyze the results.

Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving structures). When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses a least squares fitting algorithm that computes the optimum translation and

rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number, given in angstroms, is reported by QUANTA.

- 5 One skilled in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with a target. Again, these methods require no elucidation for the skilled person but are described here for the benefit of the unskilled reader. The screening process may begin by visual inspection of the target on the computer screen, generated from a machine-readable storage medium.
- 10 Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within that binding pocket as defined supra. Docking may be accomplished using software such as Quanta and Sybyl, followed by energy minimization and molecular dynamics with standard molecular mechanics force fields, such as CHARMM and AMBER.

15

Specialized computer programs may also assist in the process of selecting fragments or chemical entities. These include:

1. GRID (P. J. Goodford, "A Computational Procedure for Determining Energetically
20 Favorable Binding Sites on Biologically Important Macromolecules", J. Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.
2. MCSS (A. Miranker et al., "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." Proteins: Structure, Function and Genetics, 11, pp.
25 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, Mass.
3. AUTODOCK (D. S. Goodsell et al., "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure, Function, and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from Scripps Research Institute, La Jolla,
30 Calif.

4. DOCK (I. D. Kuntz et al., "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from University of California, San Francisco, Calif.

- 5 Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound or complex. Assembly may be preceded by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of calcineurin. This would be followed by manual model building using software such
10 as Quanta or Sybyl.

Useful programs to aid one of skill in the art in connecting the individual chemical entities or fragments include:

1. CAVEAT (P. A. Bartlett et al, "CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules". In Molecular Recognition in
15 Chemical and Biological Problems", Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, Calif.

- 20 2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, Calif). This area is reviewed in Y. C. Martin, "3D Database Searching in Drug Design", J. Med. Chem., 35, pp. 2145-2154 (1992).

3. HOOK (available from Molecular Simulations, Burlington, Mass.).

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As the skilled reader will already know, instead of proceeding to build ligand for the target in a step-wise fashion, one fragment or chemical entity at a time as described above, inhibitory or other target-binding compounds may be designed as a whole or *de novo*. These methods include:

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interactions. Specifically, the sum of all electrostatic interactions between the inhibitor or other ligand and the target, when the inhibitor is bound to the target, preferably make a neutral or favourable contribution to the enthalpy of binding.

- 5 Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C [M. J. Frisch, Gaussian, Inc., Pittsburgh, Pa. .COPYRGT.1992]; AMBER, version 4.0 [P. A. Kollman, University of California at San Francisco, .COPYRGT.1994]; QUANTA/CHARMM [Molecular Simulations,
10 Inc., Burlington, Mass. .COPYRGT.1994]; and Insight II/Discover (Biosysm Technologies Inc., San Diego, Calif. .COPYRGT.1994). These programs may be implemented, for instance, using a Silicon Graphics workstation, IRIS 4D/35 or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known to those skilled in the art.

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Once the ligand has been optimally selected or designed, as described above, substitutions may then be made in some of its atoms or side groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, i.e., the replacement group will have approximately the same size,
20 shape, hydrophobicity and charge as the original group. It should, of course, be understood that components known in the art to alter conformation should be avoided. Such substituted chemical compounds may then be analyzed for efficiency of fit to a calcineurin-like binding pocket by the same computer methods described in detail, above. Again, all these facts are familiar to the skilled person.

25

Another approach is the computational screening of small molecule data bases for chemical entities or compounds that can bind in whole, or in part, to a target. In this screening, the quality of fit of such entities to the binding site may be judged either by shape complementarity or by estimated interaction energy. E. C. Meng et al., J.
30 Comp. Chem., 13, pp. 505-524 (1992).

The computational analysis and design of molecules, as well as software and computer systems therefor are described in US Patent No 5,978,740 which is included herein by reference, including specifically but not by way of limitation the computer system diagram described with reference to and illustrated in Fig 3 thereof
5 as well as the data storage media diagram described with reference to and illustrated in Fig 4s and 5 thereof.

Statement of the Invention

10 According to a first aspect of the invention there is provided a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, for use in rationalised drug design. We have found that the dimer comprises residues vital for transcriptional and replicational activities of said protein lying on opposite sides of an N-terminal domain, for use in rationalised drug design.

15 Preferably the E2NT dimer protein is substantially as depicted in any of Figures 2c and/or 3a-d.

According to a second aspect of the invention there is provided an *in vitro* method for
20 identifying and/or selecting a candidate therapeutic agent, the method comprising determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation.

25 Preferably, the method is for use in identifying and/or selecting an antiviral candidate therapeutic agent.

Preferably, the candidate therapeutic agent interferes or blocks interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

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According to a third aspect of the invention there is provided use of an E2NT dimerisation inhibitor in the preparation of a medicament for use in treating warts, proliferative skin lesions and/or cervical cancer.

- 5 According to a fourth aspect of the invention there is provided a method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of warts, proliferative skin lesions and/or cervical cancer comprising taking a sample from said patient and measuring E2NT interactions and/or DNA loop formation.

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Thus it will be appreciated that a patient can be monitored at the start of therapy to test its effectiveness. Alternatively, a patient can be monitored once a therapy has been established so as to monitor its efficacy with a view to altering a therapy if found to be unsatisfactory.

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- The human papillomavirus E2 protein controls the primary transcription and replication of the viral genome. Both activities are governed by a ~200 amino acid N-terminal module (E2NT) which is connected to a DNA binding C-terminal module by a flexible linker. The crystal structure of the E2NT module from high-risk type 16
- 20 human papillomavirus reveals an L-shaped molecule with two closely packed domains, each with a novel fold. It forms a dimer in the crystal and in solution. The dimer structure is important in the interactions of E2NT with viral and cellular transcription factors and is the key to induction of DNA loops by E2. These loops may serve to target distal DNA-binding transcription factors to the region proximal to
- 25 the start of transcription. The structure has implications for antiviral drug design and cervical cancer therapy.

- The invention includes method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure
- 30 obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal structure using X-ray diffraction. The method by which the E2NT crystal

structure is obtainable may comprise crystallisation using hanging-drop vapour diffusion. The method by which E2NT crystal structure is obtainable may comprise X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing. The crystal structure may comprise
5 the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94. The rationalised drug design may comprise designing drugs which interact with the dimerisation surface of E2NT.

Further provided is a computer for producing a three-dimensional representation of a
10 molecule or molecular complex, wherein said molecule or molecular complex comprises or a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

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(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3;

20

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said
25 three-dimensional representation; and

30

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

In class of embodiments, the three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

An additional aspect of the invention resides in a computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

10

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;

15 (b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

20 (c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b)
25 into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

30 A yet further aspect of the invention relates to a crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT

amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3 or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. The molecule or molecular complex may be defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

27. A machine-readable data storage medium (e.g. a magnetic or optical storage medium, for example a hard disc, a floppy disc or a CD-ROM), comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

In the machine-readable data storage medium the molecule or molecular complex may be defined by the set of structure coordinates according to Table 3, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

The invention further provides a machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second

set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

5

In another aspect, the invention resides in a method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to the invention, comprising the steps of:

- 10 a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and
- b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

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Detailed Description of the Invention

The invention will now be described by way of example only with reference to the following Figures and Tables wherein:

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Table 1 illustrates X-ray data and phasing statistics;

Table 2 illustrates refinement and model correlation;

10 Table 3 shows the structure coordinates of the E2NT module;

Figure 1a represents functional assignments of HPV 16 E2 protein;

15 Figure 1b illustrates sequence alignment of E2NT modules from a subset of HPV types;

Figure 2a illustrates a stereo view of electron density with a final model at the dimer interface of the E2NT module, viewed down the crystallographic two-fold axis;

20 Figure 2b represents a stereo ribbon diagram of the E2NT module;

Figure 2c represents the E2NT dimer;

25 Figure 3a illustrates a schematic view of URR;

Figure 3b illustrates a schematic view of loop formation induced by binding of E2 proteins to two cognate sites;

Figure 3c illustrates a model of E2 dimer formation;

30

Figure 3d illustrates loops within URR as shown in Figure 3b;

Figure 4a illustrates the distribution of conserved residues on the E2NT monomer;

Figure 4b illustrates a first cluster of conserved residues on the E2NT monomer;

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Figure 4c illustrates a second cluster of conserved residues on the E2NT monomer;
and

Figure 4d illustrates conserved residues Gln12 and Glu39.

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Those of skill in the art understand that a set of structure coordinates for an enzyme or an enzyme-complex or a portion thereof, is a relative set of points that define a shape in three dimensions. Thus, it is possible that an entirely different set of coordinates could define a similar or identical shape. Moreover, slight variations
15 caused by acceptable errors in the individual coordinates will have little, if any effect on overall shape. In terms of binding pockets, these acceptable variations would not be expected to alter the nature of ligands that could associate with those pockets.

The term "associating with" refers to a condition of proximity between a chemical
20 entity or compound, or portions thereof, and a calcineurin molecule or portions thereof. The association may be non-covalent--wherein the juxtaposition is energetically favored by hydrogen bonding or van der Waals or electrostatic interactions--or it may be covalent.

25 The invention is also described with reference to US Patent No 5,978,740 which is included herein by reference, including specifically but not by way of limitation the computer system diagram described with reference to and illustrated in Fig 3 thereof as well as the data storage media diagram described with reference to and illustrated
in Fig s 4 and 5 thereof.

30

With reference to Figure 1a and functional assignments of E2. There is shown in a schematic view of NT, linker and CT modules of E2 indicating known functions of each module. Amino acid numbers which delimit the modules correspond to E2 from HPV16. In Figure 1b, there is shown the sequence alignment of the E2NT
 5 modules from a subset of HPV types (HPV16, HPV18, HPV11 and HPV2a) and one BPV type. Shaded blocks above the alignment indicate the experimentally determined secondary structure. Shaded blocks below the sequences indicate the minimal peptide sequences involved in protein:protein interactions, suggested by mutation studies. Residues with more than 90% identity among 86 PV types are
 10 coloured: red for internal structural residues, green for residues within the fulcrum region, blue for surface residues.

With reference to the structural features of E2, in Figure 2a there is shown a stereo view of the electron density with the final model, at the dimer interface of the E2NT
 15 module, viewed down the crystallographic two-fold axis. The likelihood weighted map is contoured at the 1.5 σ level. Ribbons of two independent monomers are coloured blue and yellow. Side chains of ARG37 and Ile73 which are known to be critical for transactivation^{4,31}, are shown in dark green; side chain of other residues at the dimer interface are shown in light green. Oxygen atoms are in red, nitrogen in
 20 blue, water molecules are shown as orange spheres and hydrogen bonds as dashed sticks. In Figure 2b, there is shown a stereo ribbon diagram of the E2NT module. The N1 domain is shown in aquamarine and the N2 domain in pink, with the fulcrum in green. In Figure 2c, there is shown the dimer of E2NT, showing the extent of the interface between the two subunits. The view is as in Figure 2a but rotated clockwise
 25 by 90°. Side chains of Gln12 and Glu39 which are critical for interactions with E1^{31-33,37} are shown in magenta. Side chains of residues at the dimer interface are coloured as per Figure 2a.

With reference to Figures 3a-d there is shown loop formation in the URR of HPV16.
 30 In Figure 3a, there is shown a schematic view of the URR. The four E2-binding sites are represented by boxes. Numbers in italics indicate distances between individual

sites upstream of the p97 promoter. Two possible E2 configurations, with separate or dimeric E2NT modules are shown. In Figure 3b, there is shown a schematic view of loop formation induced by binding of E2 proteins to two cognate sites, based on the experiments reported by Knight *et al*⁸. In Figure 3d, there is shown the possible DNA loops within the URR as depicted in Figure 3b. In Figure 3c, there is shown a model of the formation of E2 dimers, showing interactions between both the C-terminal and E2NT modules. The C-terminal dimer, with its bound DNA, is based on the crystal structure of this module¹². The E2NT dimer is proposed from the present work. The relative orientation and position of the E2NT and C-terminal modules is purely schematic.

With reference to Figures 4a-d there are shown functionally important residues. In Figure 4a, there is shown the distribution of conserved residues on the E2NT monomer. In Figures 4b and 4c there is shown the two clusters of conserved residues in the fulcrum of E2NT. In Figure 4d, there are shown conserved residues Gln12 and Glu39. Bonds in ball-and stick models are coloured aquamarine (N1 domain), pink (N2 domain) and green (fulcrum). Hydrogen bonds are shown as dashed lines, water molecules as orange spheres, oxygen atoms are in red, nitrogen atoms in blue and sulphur atoms in yellow.

There is convincing evidence that the E2 protein has an extended structure, is flexible and that its functions depend on this property. This is probably the reason why the intact protein has not yet been crystallised in spite of intensive efforts. A major problem is the extended flexible linker module, with around 100 residues. E2NT proved difficult to crystallise, and a number of different constructs were made and overexpressed before crystallisation with residues 1 to 201 was achieved, but even this construct possessed limited stability. The protein had to be crystallised within 2-3 days of purification; crystals grew within about 48 hours but only retained useful diffraction quality for a further 2-3 days. This necessitated that crystals be rapidly vitrified in cryoprotectant buffer and stored for use as soon as detector time became available¹⁶.

Crystals of E2NT belong to the space group $P3_121$ with unit-cell dimensions $a=b=54.3$ Å, $c=155.5$ Å. The structure was determined using two heavy atom derivatives and refined with data extending to 1.9 Å spacing (Fig. 2a). The main chain is well defined throughout with the exception of residues 125 and 126 which are in an exposed loop and are mobile. There was density for the last residue of the His-tag at the N-terminus, but none for the remainder of this entity. All amino acids lie in the allowed regions of the Ramachandran (ϕ, ψ) plot¹⁷ with 92.4% in most favoured regions¹⁸.

10

The transactivation module is composed of two domains, N1 and N2, arranged so as to give it an overall L-shaped appearance. Analysis of the PDB¹⁹ using DALI²⁰ shows that both have unique organisation of their secondary structures. Domain N1, which forms the N-terminus of the intact E2, is composed of residues 1 to 92, which fold into three long α -helices, Figure 2 (b,c). There is a tight loop between $\alpha 1$ and $\alpha 2$ and a more extended one between $\alpha 2$ and $\alpha 3$. The three helices pack antiparallel to one another in the form of a twisted plane, with angles of about 20° and 25° between the pairs of consecutive helices. DALI indicated a maximum Z-score of 5.7, that could suggest a significant correlation, for colicin 1a, a membrane protein which contains three 80 Å long α -helices arranged more or less coplanar²¹. This is the only other known protein that contains a true domain made up of such a packing of three helices. In addition there were 42 other structures which gave Z-scores above 4.0, most of which were four helix bundles, such as bacterioferritin²². However, in these only two of the three N1 helices superimposed simultaneously on two, not always adjacent, bundle helices as a result of a more planar arrangement of helices within N1. The indications are that the similarities observed reflect the optimum stacking angle of antiparallel helices against one another rather than suggesting a common ancestor for the evolution of these molecules.

Domain N2 is made up of residues 110 to 201 and is composed almost entirely of antiparallel β structure, with only one short helical segment from residues 171 to 178,

Figure 2 (b,c). The secondary structure has two short three and four stranded antiparallel β pleated sheets interconnected by two stranded β ribbons. For this domain DALI failed to identify any significant homologies to known structures, with a highest Z-score of only 2.1. From the analysis of Harris and Botchan¹⁵ and the present study, the N2 fold appears to be novel.

The structure between the N1 and N2 domains (residues 93 to 109) contains two consecutive single turns of helical structure, resulting in a compact and tight turn. It packs closely against elements of both domains and is not a truly independent structural domain. Rather it forms a fulcrum in the L-shape formed by N1 and N2 where it could act as a hinge, allowing the two domains to change their relative conformation in a specific way. Several of the interactions between adjacent regions of chain in the fulcrum are mediated indirectly through H-bonds involving water molecules, suggesting the possibility of flexibility.

One of the most striking features of the crystal structure is the association of two E2NT monomers into a tight dimer. The two E2NT monomers pack around the crystallographic 2-fold axis, as shown in Figure 2a. The dimer interface is formed mostly by amino acids from helices $\alpha 2$ and $\alpha 3$ of the N1 domain and by residues 142-144 from the N2 domain. The total buried surface area between the two E2NT is 2026 \AA^2 , comparable to the 2444 \AA^2 buried between the two E2CT¹², which are known to form a tight dimer with a K_d of $3-6 \times 10^{-8} \text{ M}$ ^{23,24}.

In the E2NT dimer interface, each subunit contributes a cluster of seven equivalent residues, invariant or conserved in the 86 known sequences of E2¹¹, with many direct and water-mediated hydrogen bonds and rather few non-polar contacts, Fig. 2. Analysis of the dimer forming surfaces shows that all the direct hydrogen bonds between monomers are made through these seven amino acids. For the invariant Arg37, all possible side-chain hydrogen bonds are made and all are well defined, Figure 2. Three of them are across the dimer interface. One hydrogen bond is critical, from NH2 to the main chain carbonyl oxygen of Leu77. A second hydrogen bond from NH2 is to OG1 of Thr81; in five out of 86 sequences this residue is

glutamine, and modelling shows a hydrogen bond is possible to the NE of Arg37. The NH1 of Arg71 H-bonds to the OE1 of residue 80, which is Glu or Gln in all but six variants. At the NE of Arg37 there is an ideal H-bond to water that itself makes another strong H-bond across the dimer interface to the main-chain carbonyl oxygen of residue 142. The role of the invariant Ile73 is the filling of the intersubunit non-polar volume made up of the aliphatic parts of Arg37, Gln76 and of Leu77 - in this case from both monomers. The Leu77 is in a few sequences substituted by valine or isoleucine and in 9 out of 86 known sequences by methionine. Inspection of the structure shows that Leu77 is partially exposed to the solvent and therefore different hydrophobic side chains could be easily accommodated at this site. Another important non-polar side chain is Ala69. Its side chain methyl packs into the surface of the other monomer at van de Waals distance from the main chain of residue 142. The only observed mutation of Ala69 is to Gly, and is easily accommodated. Gln76 is conserved or has homologous substitutions in about 2/3 of E2 sequences; in about 1/4 of the sequences there is methionine or valine at this position¹¹. Although hydrophobic substitutions of Gln76 would disrupt the hydrogen bonding to Glu80 across the dimer interface, and to Arg37 from the same subunit, the hydrophobic side chain at residue 76 could instead make a compensating hydrophobic interaction with the adjacent intersubunit hydrophobic pocket formed by Ile73 and Leu77.

Modelling of the amino acid variations in the 86 known papillomavirus E2 proteins into the other contacts at the dimer interface shows that they generally can be accommodated (data not shown). The consistency of the hydrogen bonds and van de Waals contacts at the monomer-monomer interface in the various sequences suggests therefore that the E2NT dimer interactions are potentially present in all papillomaviruses.

The first experimental evidence for the E2NT dimerisation in the presence of DNA with multiple E2-binding sites was provided by Knight *et al* in 1991⁸. Their studies showed that intact E2 led to the formation of DNA loops on templates with widely separated E2 binding sites, while a truncated E2, containing the DNA-binding E2CT but missing the N-terminal 161 residues, did not. Such dimerisation is further

supported by the observed synergistic transcription activation by a complex of two DNA-bound E2 dimers²⁵.

To analyse the functional behaviour of the E2NT dimers further, we measured the dissociation constant by sedimentation equilibrium using analytical ultracentrifugation of recombinant E2NT protein containing the 201 N-terminal amino acids. A value of $K_d = 8.1 \pm 4 \times 10^{-6}$ M was obtained, indicating medium-strength association. The micromolar range of the E2NT dimer K_d is certainly physiologically significant, and compares well with values for other transcription factors which have relatively low dissociation constants, often with the K_d values between 1 μ M and 20 μ M^{26,27}. *In vivo*, the interaction could be enhanced when the two E2NT modules are placed in close proximity. Indeed, E2CT forms dimers which bind to the multiple DNA-binding sites located within the URR of viral DNA with K_d of protein:DNA interactions usually in the nanomolar range²⁸. Consequently, the local concentration of E2NT, bound to the E2CT via the non-conserved, flexible ~80 amino-acid linker, is effectively increased.

E2NT dimer interactions, as seen in the crystal structure, could form either between modules which are already part of a single E2 dimer, formed as a result of E2CT dimerisation interactions and bound to a single E2 binding site on the DNA (Fig. 3a), or between two preformed E2 dimers located on different E2 binding sites (Fig. 3b). The results of the electron microscopy suggest that the latter dimerisation does occur⁸. Although no direct experimental evidence exists for the former dimerisation, it does also seem possible due to the flexibility of the linker connecting the two modules. We propose that E2 molecules may initially keep their N-terminal modules within their internal dimers, but swap N-terminal modules and cross link to E2 molecules bound to distant DNA binding sites to form active loop structures during transcriptional activation and / or HPV DNA replication (Figure 3d). As discussed below, the effects of mutations on transcriptional transactivation can be explained in terms of the dimer being an essential element in this process.

E2 is a regulator of both transcription and viral DNA replication and thus interacts with other viral and host macromolecules in the infected cell. Indication of the possible importance of individual residues in the function comes firstly from the structure, secondly from the extensive set of sequences of the papillomaviral E2's and thirdly from mutagenesis studies on the individual proteins. In the following we make a primary attempt to map the molecule's function onto its structure.

The pattern of amino acid conservation for the 86 available papilloma sequences¹¹ has been analysed using the GCG program suite²⁹. The sequences exhibit striking variation, characteristic of some virus families. However, 33 of the total 201 residues in the E2NT construct were totally or highly conserved. Fig. 4a illustrates the distribution of these 33 residues in the dimer. These were categorised into two sets: those with an essentially structural role and those exposed on the surface with a potential for intermolecular interactions. Thirteen residues (Fig. 1b) are buried or play a purely structural role within the monomer, they are not expected to be of functional importance and will not be discussed here.

A further 12 of these 33 residues stand out as having a structural role in the interface of the N1 and N2 domains. They form three clusters, the first making direct interactions between the two domains (Ile82, Glu90, Trp92, Lys112, Tyr138, Val145) and two separate sets of interactions, one from N2 (Pro106, Lys111, Phe168, Trp134) and the other from N1 (Trp33, Leu94) to the structure connecting them, referred to here as a fulcrum. The first two clusters are shown in Figure 4 b, c and it can be seen that Lys111 and Lys112 play key roles. Their side chains point in opposite directions to one another and their terminal amino groups are involved in near ideal patterns of hydrogen bonds. The flat surfaces of their extended side chains stack against Trp134 and Trp92, respectively. This clustering of invariant residues at the interface indicates a functional importance for the relative orientation of N1 and N2. The fulcrum could indeed provide a flexible pivot between the two domains, but there is no direct evidence for this as yet. Finally, while the side chain of Glu90 is held tightly in place by two H-bonds and could have a structural role, its OE2 atom is

exposed on the surface and is surrounded by near invariant side-chains, which may thus play a part in interactions with other molecules.

Of the remaining eight conserved residues, mutational substitutions of Glu20, Glu100 and Asp122³⁰⁻³³ had moderate effects on the transactivation and replication properties of E2, which depended on a particular viral strain. Glu20 lies on the top surface of N1. Asp122 lies far away on the distal surface of N2. Glu100 is completely exposed and points into the solvent at the junction of the L between the N1 and N2 domains. The functional role of these amino acids has yet to be clarified.

10

Three conserved amino acids (Arg37, Glu39 and Ile73) have been subjected to point mutation and the effects on the two principal functions of E2, i.e. transactivation and HPV DNA replication have been assessed (reviewed in⁴, also^{31,34,35}). Together with the remaining two conserved amino acids, Gln12 and Ala69, these residues form two functionally important surfaces (see below).

15

Finally, a number of the mutational results (reviewed in⁴, also^{31,34,35}) correspond to residues that can be assigned to structural roles. Substitution of these residues will lead to substantial conformational changes and a probable inability to fold correctly. This is particularly true for some of the deletion mutants involving the core of the molecule. Knowledge of the structure will allow a more rational choice and design of mutants in the future.

20

The induction of DNA loops by E2NT dimerisation could be important for the construction of the active transcription bubble by targeting DNA-binding transcription factors, bound at distal sites, to the region proximal to the start of transcription (reviewed in³⁶). In support of this, residues Arg37, Ile73 and Gln76 map onto the surface of E2NT involved in dimer formation, and mutations result in considerable disruption of transactivation, while having little effect on replication,^{4,15,31}. The structure also shows that Ala69 which points its side chain methyl across the dimer interface, is also critical for transactivation. Mutational substitutions to

30

amino acids with longer side chains should have a knock out effect on E2NT dimer formation and consequently on transactivation.

The sites of association with cellular transcription factors AMF-1 (residues 74-134) and TFIIB (134-216) were previously mapped onto the E2NT module (Figure 1) using a series of deletion mutants as well as point mutations^{34,35}. These sites were mutually exclusive. In the structure, residues 74-134 include the fulcrum, while residues 134-216 correspond to domain N2. Further biochemical and structural studies can now be planned to characterise these interactions in more detail.

Replication of the viral genome is initiated by binding of another viral protein, E1, to the origin of DNA replication⁴ which is itself flanked by two E2 binding sites, Fig. 3a. While the function of E2CT dimers is to bind specifically to the DNA sites, E2NT interaction with E1 enhances the binding of E1 to this region. Mutational substitutions of Glu39 generally retained transcriptional activation while DNA replication was substantially reduced^{31-33,37}. In the structure, the conserved Glu39 makes every possible hydrogen bond by its side chain carboxyl oxygens, Fig. 4d. One hydrogen bond is to NE2 of Gln12, which is absolutely conserved in all known sequences of E2. The other three hydrogen bonds are to the water molecules which are part of an intimate net of well-defined water molecules surrounding Glu39 and mediating its interactions with adjacent residues. Interestingly, a number of these protein interactions with water molecules are conserved as they are made to the protein backbone, including carbonyl oxygens of Gln12, Met36 and Lys68. While mutation of Gln12 in BPV1 only slightly affected both transactivation and replication, it substantially reduced cooperative origin binding^{30,32}. The close positioning of Gln12 and Glu39 in the three-dimensional structure further enhances the notion that these two residues are involved in interactions with E1. The conserved set of interactions at Gln12/Glu39 suggests that the main chain carbonyl oxygens of Gln12 and Met36 and the conserved water molecules could be also involved in these interactions. Gln12/Glu39 are surrounded by Leu8, Ile15, Met36, Tyr43, Gln57 and

Lys68, which are unlikely to contribute into E2/E1 interactions, as these residues are not well conserved in E2 sequences from different papillomaviruses.

5 The Gln12/Glu39 cluster lies on a side of the N1 domain which is opposite to the side involved in transactivation (and dimerisation), Figure 2c. Notably, the spatial separation of the two functionally important surfaces suggests that E2NT module could be able to interact with E1 at the same time as it interacts through the dimerisation interface with another E2NT module.

10 The structure reported here for the entire E2 transactivation module, has several implications for understanding of E2 function. It is now possible to map known mutations onto the E2 three-dimensional structure, and to use the knowledge of amino acid conservation and the effects of mutations to assign roles in folding, structure and function to residues. To this end, our results indicate that molecular
15 surfaces involved in transactivation and E1-binding are located at opposite sides of the N1 domain of E2NT, suggesting that both surfaces could be accessed simultaneously by other protein factors. In line with these observations, E1 has been shown to modulate transactivation by directly interacting with E2, leading to repression of transactivation in the presence of excess E1³⁸. It is not inconceivable
20 that the docking of E2NT dimer with E1 is sufficient to block further association with other target proteins.

The structure shows that the transactivation surface is involved in the formation of the E2NT dimer, which could cross-link E2 molecules bound by their E2CT modules
25 to well-separated DNA sites. Inevitably, such dimerisation would cause DNA to form a loop structure, targeting distally bound transcription factors to regions close to the promoter. While this process has been suggested to be essential for transactivation³⁶, the definition of interacting surfaces between E2 and other cellular transcription factors requires a great deal of further study.

30

Our results suggest that the process of DNA loop formation could involve swapping of E2NT modules across E2 dimers bound at separated DNA sites (Fig. 3a-d). The polar components of the monomer-monomer interactions may favour such exchange. Domain swapping is a well-recognised phenomenon that occurs relatively frequently
5 between two individual monomers containing domains connected by a flexible linker^{39,40}. E2 is to our knowledge the first example where the swapping event is predicted to occur between dimers.

The dimerisation surface of E2 represents a good target for designing anti-viral drugs,
10 since it is essential for viral transcription, there is no homologous human protein and the residues forming the interface are highly conserved among different viral strains. Dynamic interactions between transcription factors play a central role in the regulation of transcription and replication. Dimerisation, heterodimerisation and the monomer-to-dimer transition may play important roles during the control of the
15 papillomavirus life cycle. These processes themselves can be regulated through phosphorylation, proteolysis, interaction with small ligands or changes in their intracellular concentration. It has been suggested that E2 can regulate the switch between early gene expression and viral genome replication during HPV infection⁴¹. It is possible that dimerisation of E2NT modules plays an essential role during this
20 process. One scenario would be to activate transcription via induction of DNA loop formation at early stages of the viral life cycle. At later stages, when the concentration of expressed E2 proteins within the cell becomes high and comparable with the K_d for E2 dimer formation, free E2NT modules could compete for dimerisation with those involved in DNA loop formation and titrate them away,
25 switching off transcription and stimulating replication. It is also possible that other protein factors could be involved in this process, including, for example, E1.

The invention therefore includes the use of E2NT crystal structure in the design of anti-viral drugs, since it is essential for viral transcription. In the rationalised
30 computational design of drugs using the crystal structure, computational analyses are therefore necessary to determine whether a molecule or the E2NT-binding portion

thereof is sufficiently similar to the E2NT structure. Such analyses may be carried out in current software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., Waltham, Mass.) version 3.3, and as described in the accompanying User's Guide, Volume 3 pages. 134-135.

5

The Molecular Similarity application permits comparisons between different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: 1) load the structures to be compared; 2) define the atom
10 equivalences in these structures; 3) perform a fitting operation; and 4) analyze the results.

Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving
15 structures). Atom equivalency within QUANTA is defined by user input and, for the purpose of this invention equivalent atoms may be defined as protein backbone atoms (N, C.alpha., C and O) for all conserved residues between the two structures being compared. We will also consider only rigid fitting operations.

20 When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses a least squares fitting algorithm that computes the optimum translation and rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number,
25 given in angstroms, is reported by QUANTA.

For the purpose of one class of embodiments this invention, any set of structure coordinates of a molecule or molecular complex that has a root mean square deviation of conserved residue backbone atoms (N, C.alpha., C, O) of less than 1.5
30 .ANG. when superimposed--using backbone atoms--on the relevant structure coordinates of E2NT are considered identical. More preferably, the root mean square

deviation is less than 1.0 .ANG.. Most preferably, the root mean square deviation is less than 0.5 .ANG..

5 The term "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean. It is a way to express the deviation or variation from a trend or object. For purposes of this invention, the "root mean square deviation" defines the variation in the backbone of a protein from the backbone of E2NT a dimerising portion thereof, for example as defined by the structure coordinates of E2NT described herein.

10

The term "least squares" refers to a method based on the principle that the best estimate of a value is that in which the sum of the squares of the deviations of observed values is a minimum.

15 **Materials and Methods**

Purification and crystallisation.

Details of the purification and crystallisation of E2NT have been described previously¹⁶. Briefly, the ORF encoding the N-terminal 201 residues of HPV-16 E2 was cloned into the prokaryotic expression plasmid pET15b downstream of the 20-
20 residue His-tag leader sequence; protein was expressed in *E. coli* BL21(DE3)pLysS and purified using nickel affinity and anion exchange chromatography. Crystals were obtained by hanging drop vapour diffusion with 0.8-1.2M ammonium sulphate, 0.1M triethanolamine pH 8.0-8.3 and 3-5% 2-methyl-2,4-pentanediol. Crystals grew only with very fresh protein preparations and deteriorated in terms of diffraction quality in
25 less than a week. This necessitated freezing and storage of crystals in liquid nitrogen immediately after growth, as discussed above.

Structure determination.

All data were recorded on cryogenically frozen crystals. A native crystal was frozen for which initial data were recorded to 3.4 Å¹⁶. For the screening of derivatives,

crystal stability was even more limiting. Nine crystals were soaked in various heavy atom reagents immediately after growth. The crystals were screened in-house using a MAR research imaging plate on a Rigaku RU200 rotating anode source, by recording 3° of data for each and analysing the fractional isomorphous difference from the native. Three derivatives showed promising differences from the native, in the range of 15-20% after scaling using SCALEPACK⁴² and were stored in liquid nitrogen. The native crystal was transported to EMBL Hamburg where 1.9 Å data were measured using synchrotron radiation from beam line X11, Table 1. In addition data were recorded at EMBL for the three promising derivatives to about 2.7 Å. Two of these derivatives proved useful in phase determination and the structure was solved by multiple isomorphous replacement with anomalous scattering (MIRAS) at 2.7 Å. The two derivatives were solved independently using the CCP4 suite⁴³ from the difference Patterson synthesis and by direct methods as implemented in SHELX⁴⁴. Both contained a single heavy atom site. Phases, calculated using MLPHARE, were enhanced by solvent flattening⁴⁵ using a solvent content of 50 %. The resulting high quality density map was easily interpretable and the initial model was built using QUANTA (Molecular Simulations) for all but four residues of the construct, ignoring the His-tag. The model was completed with REFMAC (resolution 20-1.9 Å) using a bulk solvent correction, to an R-factor of 23.3 % (R_{Free} 29.7 % - for 5 % of the data). There are 221 residues in the recombinant protein: the first twenty comprise the His-Tag. The final model contains all but two of the 201 residues of the real protein: residues 125-126 are disordered and lie in a flexible surface loop. Only one residue, His0, of the His-tag has clear density and an ordered conformation. In addition there are 187 water molecules, which were selected using ARP⁴⁶ during the course of refinement. The main statistics of the refined model are shown in Table 2.

Analytical ultracentrifugation.

Experiments were carried out in an Optima XL-A ultracentrifuge (Beckman-Coulter, CA, USA) using scanning UV optics. During the experiments, the recombinant E2NT was in 10mM TrisHCl pH 8.0, 5mM DTT, 0.2 mM EDTA, 300 mM NaCl.

Data were obtained at rotor speeds of 12,000 and 16,000 rpm, and the time to equilibrium was 10-12 hours. All runs were carried out at 293K, and all radial scans were at a wavelength of 280 nm. Dissociation constants were obtained by nonlinear regression using the Beckman ultracentrifuge software.

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Table 1

X-ray data and phasing statistics

Data set	Native	UAc	AuCN
Space Group	P3 ₁ 21	P3 ₁ 21	P3 ₁ 21
a ,b (Å)	54.68	54.49	54.58
c (Å)	155.73	155.66	156.50
Resolution (Å)	30-1.9	20-2.7	20 - 2.7
Temperature, K	120	120	120
Wavelength (Å)	0.86	0.86	0.86
Unique reflections	21751	7873	7937
Completeness (%) (outer shell)	98.8 (89.3)	99.8 (96.1)	99.7 (93.8)
R-merge (outer shell)	0.058 (0.339)	0.073 (0.271)	0.061 (0.268)
Phasing Power: (centric / acentric)		1.55 / 2.07	0.95 / 1.40
FOM: MIRAS		0.59	
FOM: DM 20-2.7 Å (2.7 - 1.9 Å)		0.88 (0.61)	
DM: Mean phase change (20-2.7 Å)		32 °	
R-factor (FreeR)	0.223 (0.295)		

Table 2

Refinement and model correlation

	Resolution	1.9 – 10.0 Å
	Number of protein atoms	1622
5	Number of solvent sites	211
	Number of reflections used in refinement	20637
	Number of reflections used for Rfree calculation	1111
	R-factor [†]	0.232
	Rfree [†]	0.305
10	Average atomic B-factor*, Å ²	
	protein atoms	38.0
	water molecules	48.5
	R.m.s. deviations from ideal geometry (Å). Targets in parentheses	
	bond distance	0.013 (0.020)
	angle distance	0.026 (0.040)
15	chiral volume	0.142 (0.200)

[†]Crystallographic R-factor, $R(\text{free}) = \sum ||F_o| - |F_c|| / \sum |F_o|$.

20

Table 3

	CRYST	54.680	54.680	155.730	90.00	90.00	120.00	P3121
	SCALE1	0.01829	0.01056	0.00000			0.00000	
25	SCALE2	0.00000	0.02112	0.00000			0.00000	
	SCALE3	0.00000	0.00000	0.00642			0.00000	
	ATOM	1	N	HIS	A	0	5.469 -26.512	52.262 1.00 61.92
	ATOM	2	CA	HIS	A	0	6.434 -25.669	51.568 1.00 61.84
	ATOM	3	C	HIS	A	0	6.263 -25.743	50.051 1.00 53.91
30	ATOM	4	O	HIS	A	0	6.089 -24.713	49.607 1.00 69.59
	ATOM	5	CB	HIS	A	0	7.837 -26.127	51.965 1.00 54.18
	ATOM	6	CG	HIS	A	0	7.848 -26.468	53.431 0.00 99.00
	ATOM	7	ND1	HIS	A	0	7.914 -25.533	54.412 0.00 99.00
	ATOM	8	CD2	HIS	A	0	7.732 -27.728	54.027 0.00 99.00
35	ATOM	9	CE1	HIS	A	0	7.828 -26.215	55.570 0.00 99.00
	ATOM	10	NE2	HIS	A	0	7.723 -27.531	55.370 0.00 99.00
	ATOM	11	N	MET	A	1	6.663 -26.896	49.478 1.00 56.24
	ATOM	12	CA	MET	A	1	6.435 -27.076	48.053 1.00 56.42
	ATOM	13	C	MET	A	1	5.209 -26.282	47.619 1.00 56.07
40	ATOM	14	O	MET	A	1	5.293 -25.299	46.911 1.00 56.51
	ATOM	15	CB	MET	A	1	6.216 -28.565	47.788 1.00 60.46
	ATOM	16	CG	MET	A	1	6.856 -29.020	46.477 0.00 99.00
	ATOM	17	SD	MET	A	1	7.244 -30.775	46.483 0.00 99.00
	ATOM	18	CE	MET	A	1	7.499 -30.975	44.711 0.00 99.00
45	ATOM	19	N	GLU	A	2	4.035 -26.755	48.064 1.00 54.92
	ATOM	20	CA	GLU	A	2	2.803 -26.044	47.744 1.00 53.59

	ATOM	142	C	THR	A	17	-0.232	-5.916	36.173	1.00	54.28
	ATOM	143	O	THR	A	17	-0.860	-5.026	35.590	1.00	54.21
	ATOM	144	CB	THR	A	17	-1.677	-7.468	37.468	1.00	55.51
	ATOM	145	OG1	THR	A	17	-2.321	-8.742	37.469	1.00	54.73
5	ATOM	146	CG2	THR	A	17	-2.713	-6.355	37.551	1.00	52.35
	ATOM	147	N	HIS	A	18	0.879	-5.647	36.878	1.00	53.99
	ATOM	148	CA	HIS	A	18	1.495	-4.331	36.754	1.00	54.39
	ATOM	149	C	HIS	A	18	1.960	-4.115	35.313	1.00	55.01
10	ATOM	150	O	HIS	A	18	1.722	-3.036	34.757	1.00	54.91
	ATOM	151	CB	HIS	A	18	2.663	-4.168	37.735	1.00	53.19
	ATOM	152	CG	HIS	A	18	2.198	-3.867	39.130	1.00	52.86
	ATOM	153	ND1	HIS	A	18	1.486	-2.733	39.432	1.00	52.60
	ATOM	154	CD2	HIS	A	18	2.362	-4.553	40.296	1.00	52.72
	ATOM	155	CE1	HIS	A	18	1.216	-2.720	40.730	1.00	53.99
15	ATOM	156	NE2	HIS	A	18	1.735	-3.817	41.269	1.00	53.27
	ATOM	157	N	TYR	A	19	2.580	-5.122	34.721	1.00	56.14
	ATOM	158	CA	TYR	A	19	3.044	-5.034	33.337	1.00	58.17
	ATOM	159	C	TYR	A	19	1.890	-4.733	32.380	1.00	58.92
	ATOM	160	O	TYR	A	19	1.957	-3.827	31.552	1.00	59.36
20	ATOM	161	CB	TYR	A	19	3.759	-6.320	32.950	1.00	59.47
	ATOM	162	CG	TYR	A	19	5.097	-6.621	33.580	1.00	62.05
	ATOM	163	CD1	TYR	A	19	5.983	-5.607	33.934	1.00	63.22
	ATOM	164	CD2	TYR	A	19	5.513	-7.934	33.787	1.00	62.96
	ATOM	165	CE1	TYR	A	19	7.212	-5.891	34.488	1.00	63.58
25	ATOM	166	CE2	TYR	A	19	6.745	-8.226	34.345	1.00	63.59
	ATOM	167	CZ	TYR	A	19	7.597	-7.199	34.703	1.00	63.46
	ATOM	168	OH	TYR	A	19	8.828	-7.470	35.274	1.00	62.56
	ATOM	169	N	GLU	A	20	0.779	-5.451	32.499	1.00	59.63
	ATOM	170	CA	GLU	A	20	-0.426	-5.196	31.734	1.00	59.76
30	ATOM	171	C	GLU	A	20	-0.990	-3.804	31.918	1.00	59.59
	ATOM	172	O	GLU	A	20	-1.198	-3.103	30.928	1.00	59.90
	ATOM	173	CB	GLU	A	20	-1.499	-6.241	32.056	1.00	66.29
	ATOM	174	CG	GLU	A	20	-1.176	-7.583	31.409	1.00	73.88
	ATOM	175	CD	GLU	A	20	-2.142	-8.678	31.815	1.00	78.60
35	ATOM	176	OE1	GLU	A	20	-1.749	-9.862	31.692	1.00	82.52
	ATOM	177	OE2	GLU	A	20	-3.272	-8.365	32.242	1.00	78.94
	ATOM	178	N	ASN	A	21	-1.186	-3.340	33.145	1.00	59.04
	ATOM	179	CA	ASN	A	21	-1.784	-2.053	33.404	1.00	57.97
	ATOM	180	C	ASN	A	21	-1.002	-0.853	32.918	1.00	57.50
40	ATOM	181	O	ASN	A	21	-1.637	0.118	32.496	1.00	57.19
	ATOM	182	CB	ASN	A	21	-2.149	-1.876	34.875	1.00	61.71
	ATOM	183	CG	ASN	A	21	-3.089	-2.964	35.362	1.00	63.07
	ATOM	184	OD1	ASN	A	21	-3.691	-3.685	34.563	1.00	60.88
	ATOM	185	ND2	ASN	A	21	-3.161	-3.066	36.685	1.00	62.59
45	ATOM	186	N	ASP	A	22	0.327	-0.826	33.022	1.00	56.38
	ATOM	187	CA	ASP	A	22	1.080	0.299	32.480	1.00	54.54
	ATOM	188	C	ASP	A	22	0.710	1.630	33.112	1.00	53.00
	ATOM	189	O	ASP	A	22	0.632	2.652	32.424	1.00	52.65
	ATOM	190	CB	ASP	A	22	0.818	0.369	30.967	1.00	61.62
50	ATOM	191	CG	ASP	A	22	2.107	0.655	30.214	1.00	65.99
	ATOM	192	OD1	ASP	A	22	2.946	1.402	30.765	1.00	64.95
	ATOM	193	OD2	ASP	A	22	2.235	0.116	29.099	1.00	69.58
	ATOM	194	N	SER	A	23	0.616	1.683	34.440	1.00	50.98
	ATOM	195	CA	SER	A	23	0.213	2.879	35.148	1.00	49.25
55	ATOM	196	C	SER	A	23	1.294	3.960	35.095	1.00	48.02
	ATOM	197	O	SER	A	23	2.450	3.746	34.740	1.00	47.57
	ATOM	198	CB	SER	A	23	-0.101	2.633	36.640	1.00	46.04
	ATOM	199	OG	SER	A	23	0.549	1.424	36.984	1.00	56.16
	ATOM	200	N	THR	A	24	0.847	5.152	35.441	1.00	47.42
60	ATOM	201	CA	THR	A	24	1.724	6.312	35.512	1.00	48.00
	ATOM	202	C	THR	A	24	1.731	6.860	36.920	1.00	47.34
	ATOM	203	O	THR	A	24	2.328	7.898	37.173	1.00	47.41
	ATOM	204	CB	THR	A	24	1.369	7.421	34.505	1.00	50.50

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	ATOM	331	NH2	ARG	A	37	12.948	-5.572	52.719	1.00	32.86
	ATOM	332	N	LEU	A	38	9.920	-9.544	46.841	1.00	33.92
	ATOM	333	CA	LEU	A	38	9.330	-10.768	47.372	1.00	34.82
	ATOM	334	C	LEU	A	38	9.592	-11.985	46.532	1.00	36.08
5	ATOM	335	O	LEU	A	38	9.879	-13.050	47.066	1.00	35.88
	ATOM	336	CB	LEU	A	38	7.806	-10.549	47.542	1.00	37.00
	ATOM	337	CG	LEU	A	38	7.048	-11.843	47.862	1.00	39.41
	ATOM	338	CD1	LEU	A	38	7.338	-12.303	49.271	1.00	36.17
	ATOM	339	CD2	LEU	A	38	5.544	-11.698	47.633	1.00	42.91
10	ATOM	340	N	GLU	A	39	9.532	-11.873	45.176	1.00	36.01
	ATOM	341	CA	GLU	A	39	9.903	-12.982	44.328	1.00	35.41
	ATOM	342	C	GLU	A	39	11.310	-13.492	44.650	1.00	35.95
	ATOM	343	O	GLU	A	39	11.524	-14.706	44.610	1.00	34.71
	ATOM	344	CB	GLU	A	39	9.826	-12.621	42.814	1.00	33.83
15	ATOM	345	CG	GLU	A	39	9.999	-13.858	41.944	1.00	35.55
	ATOM	346	CD	GLU	A	39	10.153	-13.499	40.467	1.00	44.56
	ATOM	347	OE1	GLU	A	39	11.229	-12.997	40.106	1.00	42.84
	ATOM	348	OE2	GLU	A	39	9.219	-13.700	39.690	1.00	42.80
	ATOM	349	N	CYS	A	40	12.280	-12.600	44.916	1.00	35.37
20	ATOM	350	CA	CYS	A	40	13.616	-13.054	45.262	1.00	35.02
	ATOM	351	C	CYS	A	40	13.603	-13.852	46.574	1.00	35.78
	ATOM	352	O	CYS	A	40	14.329	-14.842	46.621	1.00	35.14
	ATOM	353	CB	CYS	A	40	14.587	-11.879	45.434	1.00	34.19
	ATOM	354	SG	CYS	A	40	14.743	-10.845	43.945	1.00	35.07
25	ATOM	355	N	ALA	A	41	12.796	-13.419	47.540	1.00	36.59
	ATOM	356	CA	ALA	A	41	12.772	-14.160	48.820	1.00	38.13
	ATOM	357	C	ALA	A	41	12.191	-15.553	48.590	1.00	37.52
	ATOM	358	O	ALA	A	41	12.659	-16.527	49.200	1.00	38.32
	ATOM	359	CB	ALA	A	41	11.955	-13.380	49.827	1.00	36.08
30	ATOM	360	N	ILE	A	42	11.221	-15.674	47.663	1.00	37.54
	ATOM	361	CA	ILE	A	42	10.629	-16.995	47.397	1.00	36.18
	ATOM	362	C	ILE	A	42	11.626	-17.922	46.753	1.00	36.44
	ATOM	363	O	ILE	A	42	11.856	-19.069	47.133	1.00	35.31
	ATOM	364	CB	ILE	A	42	9.325	-16.907	46.581	1.00	36.30
35	ATOM	365	CG1	ILE	A	42	8.225	-16.165	47.345	1.00	38.51
	ATOM	366	CG2	ILE	A	42	8.865	-18.282	46.108	1.00	38.23
	ATOM	367	CD1	ILE	A	42	7.114	-15.700	46.390	1.00	41.57
	ATOM	368	N	TYR	A	43	12.321	-17.436	45.707	1.00	35.53
	ATOM	369	CA	TYR	A	43	13.341	-18.254	45.060	1.00	36.20
40	ATOM	370	C	TYR	A	43	14.479	-18.536	46.047	1.00	36.21
	ATOM	371	O	TYR	A	43	15.091	-19.597	45.993	1.00	36.69
	ATOM	372	CB	TYR	A	43	13.884	-17.474	43.838	1.00	36.61
	ATOM	373	CG	TYR	A	43	13.065	-17.637	42.572	1.00	38.55
	ATOM	374	CD1	TYR	A	43	12.717	-16.512	41.820	1.00	39.59
45	ATOM	375	CD2	TYR	A	43	12.644	-18.871	42.116	1.00	39.53
	ATOM	376	CE1	TYR	A	43	11.998	-16.626	40.646	1.00	41.22
	ATOM	377	CE2	TYR	A	43	11.943	-19.006	40.918	1.00	40.40
	ATOM	378	CZ	TYR	A	43	11.604	-17.884	40.210	1.00	40.78
	ATOM	379	OH	TYR	A	43	10.847	-17.954	39.081	1.00	41.19
50	ATOM	380	N	TYR	A	44	14.794	-17.563	46.906	1.00	35.43
	ATOM	381	CA	TYR	A	44	15.933	-17.815	47.811	1.00	37.45
	ATOM	382	C	TYR	A	44	15.547	-19.008	48.716	1.00	37.65
	ATOM	383	O	TYR	A	44	16.329	-19.945	48.876	1.00	38.00
	ATOM	384	CB	TYR	A	44	16.205	-16.555	48.635	1.00	38.20
55	ATOM	385	CG	TYR	A	44	17.445	-16.670	49.503	1.00	40.09
	ATOM	386	CD1	TYR	A	44	17.398	-17.286	50.756	1.00	41.30
	ATOM	387	CD2	TYR	A	44	18.663	-16.206	49.041	1.00	40.77
	ATOM	388	CE1	TYR	A	44	18.569	-17.412	51.492	1.00	42.23
	ATOM	389	CE2	TYR	A	44	19.833	-16.312	49.776	1.00	42.80
60	ATOM	390	CZ	TYR	A	44	19.746	-16.907	51.023	1.00	43.39
	ATOM	391	OH	TYR	A	44	20.863	-17.049	51.798	1.00	45.51
	ATOM	392	N	LYS	A	45	14.334	-18.982	49.224	1.00	38.11
	ATOM	393	CA	LYS	A	45	13.891	-20.078	50.118	1.00	40.98

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	ATOM	457	NZ	LYS	A	52	20.300	-31.674	41.001	0.00	99.00
	ATOM	458	N	HIS	A	53	13.968	-26.480	40.589	1.00	46.17
	ATOM	459	CA	HIS	A	53	12.924	-25.816	39.834	1.00	45.58
	ATOM	460	C	HIS	A	53	11.697	-25.685	40.724	1.00	44.64
5	ATOM	461	O	HIS	A	53	11.566	-26.465	41.649	1.00	44.95
	ATOM	462	CB	HIS	A	53	12.568	-26.542	38.531	1.00	44.28
	ATOM	463	CG	HIS	A	53	11.635	-27.700	38.758	1.00	46.45
	ATOM	464	ND1	HIS	A	53	10.277	-27.525	38.978	1.00	45.21
10	ATOM	465	CD2	HIS	A	53	11.868	-29.026	38.829	1.00	45.27
	ATOM	466	CE1	HIS	A	53	9.709	-28.698	39.163	1.00	45.18
	ATOM	467	NE2	HIS	A	53	10.655	-29.629	39.076	1.00	49.44
	ATOM	468	N	ILE	A	54	10.895	-24.693	40.468	1.00	43.90
	ATOM	469	CA	ILE	A	54	9.598	-24.513	41.100	1.00	44.62
15	ATOM	470	C	ILE	A	54	8.589	-24.354	39.976	1.00	43.53
	ATOM	471	O	ILE	A	54	8.704	-23.454	39.123	1.00	44.50
	ATOM	472	CB	ILE	A	54	9.627	-23.258	41.996	1.00	51.01
	ATOM	473	CG1	ILE	A	54	8.222	-22.740	42.337	1.00	51.18
	ATOM	474	CG2	ILE	A	54	10.420	-22.138	41.313	1.00	54.51
	ATOM	475	CD1	ILE	A	54	8.293	-22.022	43.690	1.00	55.08
20	ATOM	476	N	ASN	A	55	7.679	-25.327	39.853	1.00	42.57
	ATOM	477	CA	ASN	A	55	6.719	-25.332	38.748	1.00	41.98
	ATOM	478	C	ASN	A	55	7.391	-25.383	37.389	1.00	41.70
	ATOM	479	O	ASN	A	55	6.958	-24.848	36.368	1.00	41.10
25	ATOM	480	CB	ASN	A	55	5.639	-24.266	38.828	1.00	41.18
	ATOM	481	CG	ASN	A	55	4.611	-24.596	39.915	1.00	45.37
	ATOM	482	OD1	ASN	A	55	4.481	-25.766	40.285	1.00	42.95
	ATOM	483	ND2	ASN	A	55	3.908	-23.589	40.393	1.00	49.59
	ATOM	484	N	HIS	A	56	8.508	-26.115	37.343	1.00	42.09
30	ATOM	485	CA	HIS	A	56	9.304	-26.336	36.155	1.00	41.80
	ATOM	486	C	HIS	A	56	9.996	-25.085	35.651	1.00	42.37
	ATOM	487	O	HIS	A	56	10.579	-25.115	34.573	1.00	41.39
	ATOM	488	CB	HIS	A	56	8.509	-27.081	35.059	1.00	38.13
	ATOM	489	CG	HIS	A	56	8.140	-28.417	35.639	1.00	39.93
35	ATOM	490	ND1	HIS	A	56	8.997	-29.476	35.683	1.00	40.64
	ATOM	491	CD2	HIS	A	56	7.000	-28.811	36.253	1.00	40.69
	ATOM	492	CE1	HIS	A	56	8.401	-30.496	36.292	1.00	46.16
	ATOM	493	NE2	HIS	A	56	7.192	-30.108	36.648	1.00	44.07
	ATOM	494	N	GLN	A	57	10.115	-24.074	36.492	1.00	42.01
40	ATOM	495	CA	GLN	A	57	10.867	-22.845	36.209	1.00	43.31
	ATOM	496	C	GLN	A	57	12.178	-22.922	37.011	1.00	42.73
	ATOM	497	O	GLN	A	57	12.135	-23.367	38.159	1.00	42.65
	ATOM	498	CB	GLN	A	57	10.017	-21.730	36.771	1.00	44.03
	ATOM	499	CG	GLN	A	57	10.191	-20.286	36.476	1.00	54.62
45	ATOM	500	CD	GLN	A	57	8.889	-19.530	36.723	1.00	54.38
	ATOM	501	OE1	GLN	A	57	8.881	-18.332	36.990	1.00	54.35
	ATOM	502	NE2	GLN	A	57	7.774	-20.248	36.641	1.00	57.38
	ATOM	503	N	VAL	A	58	13.308	-22.526	36.435	1.00	41.67
	ATOM	504	CA	VAL	A	58	14.592	-22.695	37.122	1.00	41.06
50	ATOM	505	C	VAL	A	58	14.654	-21.870	38.395	1.00	39.90
	ATOM	506	O	VAL	A	58	14.141	-20.751	38.425	1.00	40.26
	ATOM	507	CB	VAL	A	58	15.766	-22.343	36.168	1.00	41.94
	ATOM	508	CG1	VAL	A	58	15.770	-20.860	35.859	1.00	41.59
	ATOM	509	CG2	VAL	A	58	17.085	-22.872	36.676	1.00	43.75
55	ATOM	510	N	VAL	A	59	15.193	-22.451	39.461	1.00	40.08
	ATOM	511	CA	VAL	A	59	15.414	-21.673	40.713	1.00	40.24
	ATOM	512	C	VAL	A	59	16.878	-21.205	40.635	1.00	39.98
	ATOM	513	O	VAL	A	59	17.761	-22.042	40.559	1.00	41.27
	ATOM	514	CB	VAL	A	59	15.250	-22.591	41.945	1.00	40.48
60	ATOM	515	CG1	VAL	A	59	15.437	-21.777	43.243	1.00	44.12
	ATOM	516	CG2	VAL	A	59	13.830	-23.161	42.037	1.00	39.62
	ATOM	517	N	PRO	A	60	17.121	-19.911	40.686	1.00	40.13
	ATOM	518	CA	PRO	A	60	18.466	-19.380	40.576	1.00	40.49
	ATOM	519	C	PRO	A	60	19.312	-19.737	41.806	1.00	40.57

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	ATOM	646	C	LEU	A	77	13.506	4.183	47.638	1.00	34.87
	ATOM	647	O	LEU	A	77	13.070	5.221	48.149	1.00	32.77
	ATOM	648	CB	LEU	A	77	14.906	2.756	49.079	1.00	31.33
	ATOM	649	CG	LEU	A	77	14.976	1.566	50.093	1.00	33.32
5	ATOM	650	CD1	LEU	A	77	16.417	1.466	50.566	1.00	35.24
	ATOM	651	CD2	LEU	A	77	14.094	1.902	51.303	1.00	32.76
	ATOM	652	N	THR	A	78	14.094	4.162	46.440	1.00	35.43
	ATOM	653	CA	THR	A	78	14.147	5.391	45.644	1.00	35.16
10	ATOM	654	C	THR	A	78	12.754	5.938	45.407	1.00	34.62
	ATOM	655	O	THR	A	78	12.561	7.128	45.655	1.00	35.48
	ATOM	656	CB	THR	A	78	14.869	5.117	44.306	1.00	33.75
	ATOM	657	OG1	THR	A	78	16.212	4.853	44.644	1.00	36.55
	ATOM	658	CG2	THR	A	78	14.710	6.309	43.359	1.00	35.96
15	ATOM	659	N	LEU	A	79	11.867	5.059	44.971	1.00	35.23
	ATOM	660	CA	LEU	A	79	10.492	5.458	44.646	1.00	35.59
	ATOM	661	C	LEU	A	79	9.738	5.941	45.879	1.00	36.24
	ATOM	662	O	LEU	A	79	8.923	6.848	45.814	1.00	34.44
	ATOM	663	CB	LEU	A	79	9.744	4.326	43.961	1.00	37.56
	ATOM	664	CG	LEU	A	79	10.302	3.825	42.611	1.00	40.81
20	ATOM	665	CD1	LEU	A	79	9.415	2.708	42.066	1.00	36.86
	ATOM	666	CD2	LEU	A	79	10.404	4.981	41.632	1.00	44.33
	ATOM	667	N	GLU	A	80	10.058	5.284	47.023	1.00	35.96
	ATOM	668	CA	GLU	A	80	9.487	5.773	48.285	1.00	35.25
	ATOM	669	C	GLU	A	80	10.002	7.132	48.672	1.00	35.81
25	ATOM	670	O	GLU	A	80	9.241	7.941	49.182	1.00	36.57
	ATOM	671	CB	GLU	A	80	9.805	4.764	49.414	1.00	33.47
	ATOM	672	CG	GLU	A	80	8.923	3.555	49.368	1.00	36.03
	ATOM	673	CD	GLU	A	80	9.390	2.431	50.293	1.00	39.80
30	ATOM	674	OE1	GLU	A	80	10.528	2.453	50.789	1.00	38.34
	ATOM	675	OE2	GLU	A	80	8.587	1.482	50.397	1.00	40.54
	ATOM	676	N	THR	A	81	11.266	7.474	48.443	1.00	35.85
	ATOM	677	CA	THR	A	81	11.759	8.819	48.714	1.00	37.65
	ATOM	678	C	THR	A	81	11.074	9.798	47.742	1.00	39.27
	ATOM	679	O	THR	A	81	10.711	10.894	48.159	1.00	38.93
35	ATOM	680	CB	THR	A	81	13.277	8.895	48.523	1.00	38.88
	ATOM	681	OG1	THR	A	81	13.854	8.188	49.626	1.00	41.45
	ATOM	682	CG2	THR	A	81	13.827	10.315	48.511	1.00	37.76
	ATOM	683	N	ILE	A	82	10.887	9.360	46.500	1.00	39.69
	ATOM	684	CA	ILE	A	82	10.176	10.260	45.568	1.00	41.32
40	ATOM	685	C	ILE	A	82	8.727	10.458	45.979	1.00	42.17
	ATOM	686	O	ILE	A	82	8.195	11.566	45.910	1.00	42.11
	ATOM	687	CB	ILE	A	82	10.199	9.735	44.134	1.00	38.27
	ATOM	688	CG1	ILE	A	82	11.619	9.500	43.651	1.00	39.22
	ATOM	689	CG2	ILE	A	82	9.462	10.697	43.194	1.00	37.66
45	ATOM	690	CD1	ILE	A	82	12.489	10.717	43.731	1.00	43.59
	ATOM	691	N	TYR	A	83	8.097	9.376	46.426	1.00	43.95
	ATOM	692	CA	TYR	A	83	6.726	9.469	46.924	1.00	45.07
	ATOM	693	C	TYR	A	83	6.597	10.496	48.038	1.00	45.84
50	ATOM	694	O	TYR	A	83	5.613	11.234	48.097	1.00	44.82
	ATOM	695	CB	TYR	A	83	6.229	8.097	47.364	1.00	47.55
	ATOM	696	CG	TYR	A	83	4.745	8.146	47.683	1.00	52.04
	ATOM	697	CD1	TYR	A	83	3.826	8.070	46.643	1.00	53.71
	ATOM	698	CD2	TYR	A	83	4.292	8.292	48.987	1.00	53.75
	ATOM	699	CE1	TYR	A	83	2.469	8.119	46.899	1.00	55.59
55	ATOM	700	CE2	TYR	A	83	2.932	8.343	49.245	1.00	55.42
	ATOM	701	CZ	TYR	A	83	2.036	8.252	48.199	1.00	56.63
	ATOM	702	OH	TYR	A	83	0.691	8.313	48.454	1.00	58.49
	ATOM	703	N	ASN	A	84	7.594	10.600	48.932	1.00	45.54
	ATOM	704	CA	ASN	A	84	7.519	11.621	49.959	1.00	46.22
60	ATOM	705	C	ASN	A	84	7.965	12.989	49.446	1.00	45.99
	ATOM	706	O	ASN	A	84	7.812	13.930	50.226	1.00	46.80
	ATOM	707	CB	ASN	A	84	8.199	11.252	51.257	1.00	45.97
	ATOM	708	CG	ASN	A	84	7.995	9.970	52.011	1.00	42.27

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	ATOM	835	CD1	LEU	A	99	18.330	-2.481	38.442	1.00	43.84
	ATOM	836	CD2	LEU	A	99	18.341	-4.606	37.072	1.00	45.55
	ATOM	837	N	GLU	A	100	16.797	-1.199	33.818	1.00	36.41
5	ATOM	838	CA	GLU	A	100	17.488	-0.765	32.611	1.00	37.21
	ATOM	839	C	GLU	A	100	17.790	0.722	32.622	1.00	36.02
	ATOM	840	O	GLU	A	100	18.972	1.068	32.470	1.00	37.81
	ATOM	841	CB	GLU	A	100	16.690	-1.126	31.340	1.00	40.11
	ATOM	842	CG	GLU	A	100	17.528	-0.836	30.096	1.00	49.41
10	ATOM	843	CD	GLU	A	100	16.866	-1.247	28.790	1.00	56.89
	ATOM	844	OE1	GLU	A	100	15.724	-1.755	28.761	1.00	57.99
	ATOM	845	OE2	GLU	A	100	17.534	-1.025	27.753	1.00	62.25
	ATOM	846	N	VAL	A	101	16.808	1.580	32.792	1.00	35.41
	ATOM	847	CA	VAL	A	101	17.044	3.010	32.973	1.00	34.54
15	ATOM	848	C	VAL	A	101	17.897	3.329	34.185	1.00	34.62
	ATOM	849	O	VAL	A	101	18.899	4.082	34.151	1.00	33.43
	ATOM	850	CB	VAL	A	101	15.666	3.714	33.047	1.00	36.71
	ATOM	851	CG1	VAL	A	101	15.797	5.167	33.459	1.00	34.93
	ATOM	852	CG2	VAL	A	101	15.013	3.600	31.651	1.00	37.61
20	ATOM	853	N	TYR	A	102	17.555	2.678	35.314	1.00	33.28
	ATOM	854	CA	TYR	A	102	18.202	3.008	36.583	1.00	33.58
	ATOM	855	C	TYR	A	102	19.711	2.817	36.484	1.00	33.46
	ATOM	856	O	TYR	A	102	20.424	3.624	37.071	1.00	33.95
	ATOM	857	CB	TYR	A	102	17.653	2.091	37.691	1.00	34.23
25	ATOM	858	CG	TYR	A	102	17.996	2.494	39.103	1.00	36.50
	ATOM	859	CD1	TYR	A	102	17.325	3.559	39.676	1.00	36.36
	ATOM	860	CD2	TYR	A	102	18.961	1.811	39.855	1.00	36.63
	ATOM	861	CE1	TYR	A	102	17.582	3.949	40.979	1.00	37.25
	ATOM	862	CE2	TYR	A	102	19.237	2.202	41.162	1.00	37.64
30	ATOM	863	CZ	TYR	A	102	18.537	3.253	41.707	1.00	36.95
	ATOM	864	OH	TYR	A	102	18.795	3.693	42.966	1.00	36.81
	ATOM	865	N	LEU	A	103	20.170	1.800	35.766	1.00	32.90
	ATOM	866	CA	LEU	A	103	21.575	1.513	35.625	1.00	34.69
	ATOM	867	C	LEU	A	103	22.225	2.188	34.422	1.00	35.97
35	ATOM	868	O	LEU	A	103	23.434	2.037	34.247	1.00	37.11
	ATOM	869	CB	LEU	A	103	21.811	0.003	35.568	1.00	34.47
	ATOM	870	CG	LEU	A	103	21.363	-0.757	36.853	1.00	39.98
	ATOM	871	CD1	LEU	A	103	21.588	-2.261	36.702	1.00	40.37
	ATOM	872	CD2	LEU	A	103	22.104	-0.231	38.073	1.00	40.86
40	ATOM	873	N	THR	A	104	21.460	2.913	33.614	1.00	35.72
	ATOM	874	CA	THR	A	104	22.115	3.606	32.468	1.00	34.87
	ATOM	875	C	THR	A	104	22.792	4.825	33.060	1.00	35.15
	ATOM	876	O	THR	A	104	22.206	5.345	34.004	1.00	35.03
	ATOM	877	CB	THR	A	104	21.074	4.013	31.409	1.00	36.04
45	ATOM	878	OG1	THR	A	104	20.507	2.790	30.928	1.00	34.78
	ATOM	879	CG2	THR	A	104	21.709	4.722	30.211	1.00	36.74
	ATOM	880	N	ALA	A	105	23.907	5.292	32.541	1.00	35.32
	ATOM	881	CA	ALA	A	105	24.595	6.446	33.150	1.00	36.34
	ATOM	882	C	ALA	A	105	23.662	7.647	33.117	1.00	36.12
50	ATOM	883	O	ALA	A	105	23.031	7.852	32.074	1.00	35.49
	ATOM	884	CB	ALA	A	105	25.840	6.710	32.281	1.00	36.09
	ATOM	885	N	PRO	A	106	23.556	8.404	34.195	1.00	35.90
	ATOM	886	CA	PRO	A	106	24.273	8.154	35.428	1.00	36.06
	ATOM	887	C	PRO	A	106	23.617	7.057	36.275	1.00	35.41
55	ATOM	888	O	PRO	A	106	22.426	7.141	36.602	1.00	34.13
	ATOM	889	CB	PRO	A	106	24.167	9.484	36.175	1.00	36.61
	ATOM	890	CG	PRO	A	106	22.880	10.077	35.695	1.00	36.41
	ATOM	891	CD	PRO	A	106	22.862	9.725	34.223	1.00	36.94
	ATOM	892	N	THR	A	107	24.407	6.045	36.646	1.00	35.50
60	ATOM	893	CA	THR	A	107	23.833	4.857	37.287	1.00	34.62
	ATOM	894	C	THR	A	107	23.256	5.142	38.651	1.00	34.93
	ATOM	895	O	THR	A	107	23.639	6.108	39.324	1.00	34.98
	ATOM	896	CB	THR	A	107	24.820	3.666	37.301	1.00	39.51
	ATOM	897	OG1	THR	A	107	24.114	2.516	37.812	1.00	36.86

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	ATOM	1024	CA	ASP	A	124	30.122	10.180	9.717	1.00	82.77
	ATOM	1025	C	ASP	A	124	30.000	9.574	8.324	1.00	82.74
	ATOM	1026	O	ASP	A	124	29.673	9.777	7.400	0.00	99.00
5	ATOM	1027	CB	ASP	A	124	28.828	10.863	10.141	1.00	87.39
	ATOM	1028	CG	ASP	A	124	27.968	9.968	11.019	1.00	91.94
	ATOM	1029	OD1	ASP	A	124	28.495	8.933	11.489	1.00	93.18
	ATOM	1030	OD2	ASP	A	124	26.779	10.288	11.244	1.00	93.68
	ATOM	1031	N	ASN	A	127	34.160	6.401	13.268	1.00	58.22
10	ATOM	1032	CA	ASN	A	127	33.743	5.964	14.601	1.00	58.81
	ATOM	1033	C	ASN	A	127	32.728	6.983	15.144	1.00	58.26
	ATOM	1034	O	ASN	A	127	33.132	8.096	15.487	1.00	58.82
	ATOM	1035	CB	ASN	A	127	34.919	5.955	15.579	1.00	58.33
	ATOM	1036	CG	ASN	A	127	35.959	4.889	15.347	1.00	62.63
15	ATOM	1037	OD1	ASN	A	127	35.660	3.697	15.490	1.00	64.16
	ATOM	1038	ND2	ASN	A	127	37.179	5.307	15.008	1.00	60.87
	ATOM	1039	N	THR	A	128	31.462	6.617	15.180	1.00	57.71
	ATOM	1040	CA	THR	A	128	30.411	7.522	15.665	1.00	57.23
	ATOM	1041	C	THR	A	128	29.652	6.846	16.795	1.00	56.48
20	ATOM	1042	O	THR	A	128	29.065	5.792	16.534	1.00	57.24
	ATOM	1043	CB	THR	A	128	29.452	7.842	14.501	1.00	56.65
	ATOM	1044	OG1	THR	A	128	30.208	8.579	13.536	1.00	57.99
	ATOM	1045	CG2	THR	A	128	28.244	8.653	14.901	1.00	56.34
	ATOM	1046	N	MET	A	129	29.705	7.406	18.002	1.00	54.99
25	ATOM	1047	CA	MET	A	129	29.082	6.817	19.175	1.00	52.19
	ATOM	1048	C	MET	A	129	27.768	7.511	19.533	1.00	50.42
	ATOM	1049	O	MET	A	129	27.588	8.705	19.319	1.00	48.93
	ATOM	1050	CB	MET	A	129	30.009	6.909	20.391	1.00	58.00
	ATOM	1051	CG	MET	A	129	31.164	5.934	20.458	1.00	62.68
30	ATOM	1052	SD	MET	A	129	30.652	4.263	20.904	1.00	68.26
	ATOM	1053	CE	MET	A	129	29.906	4.518	22.510	1.00	68.01
	ATOM	1054	N	HIS	A	130	26.859	6.735	20.126	1.00	49.01
	ATOM	1055	CA	HIS	A	130	25.554	7.194	20.571	1.00	47.13
	ATOM	1056	C	HIS	A	130	25.485	7.057	22.095	1.00	46.21
35	ATOM	1057	O	HIS	A	130	26.009	6.118	22.678	1.00	45.61
	ATOM	1058	CB	HIS	A	130	24.436	6.345	19.956	1.00	53.82
	ATOM	1059	CG	HIS	A	130	23.967	6.751	18.602	1.00	62.48
	ATOM	1060	ND1	HIS	A	130	24.816	7.119	17.581	1.00	66.97
	ATOM	1061	CD2	HIS	A	130	22.711	6.825	18.084	1.00	65.45
40	ATOM	1062	CE1	HIS	A	130	24.114	7.424	16.505	1.00	67.80
	ATOM	1063	NE2	HIS	A	130	22.831	7.252	16.784	1.00	68.13
	ATOM	1064	N	TYR	A	131	24.998	8.097	22.775	1.00	43.95
	ATOM	1065	CA	TYR	A	131	24.923	8.130	24.227	1.00	42.51
	ATOM	1066	C	TYR	A	131	23.536	8.666	24.576	1.00	41.94
45	ATOM	1067	O	TYR	A	131	22.956	9.497	23.829	1.00	41.77
	ATOM	1068	CB	TYR	A	131	25.948	9.151	24.762	1.00	42.89
	ATOM	1069	CG	TYR	A	131	27.390	8.830	24.392	1.00	42.97
	ATOM	1070	CD1	TYR	A	131	27.910	9.421	23.240	1.00	42.76
	ATOM	1071	CD2	TYR	A	131	28.205	7.993	25.131	1.00	43.24
50	ATOM	1072	CE1	TYR	A	131	29.207	9.187	22.828	1.00	44.91
	ATOM	1073	CE2	TYR	A	131	29.502	7.765	24.728	1.00	45.47
	ATOM	1074	CZ	TYR	A	131	29.991	8.365	23.587	1.00	46.72
	ATOM	1075	OH	TYR	A	131	31.295	8.087	23.222	1.00	49.71
	ATOM	1076	N	THR	A	132	22.979	8.297	25.721	1.00	40.16
55	ATOM	1077	CA	THR	A	132	21.666	8.825	26.098	1.00	37.97
	ATOM	1078	C	THR	A	132	21.835	9.967	27.066	1.00	37.49
	ATOM	1079	O	THR	A	132	22.535	9.779	28.077	1.00	38.05
	ATOM	1080	CB	THR	A	132	20.792	7.731	26.746	1.00	38.81
	ATOM	1081	OG1	THR	A	132	20.603	6.712	25.757	1.00	36.51
60	ATOM	1082	CG2	THR	A	132	19.452	8.267	27.216	1.00	36.18
	ATOM	1083	N	ASN	A	133	21.212	11.104	26.792	1.00	35.61
	ATOM	1084	CA	ASN	A	133	21.188	12.167	27.803	1.00	36.33
	ATOM	1085	C	ASN	A	133	19.749	12.266	28.321	1.00	35.53
	ATOM	1086	O	ASN	A	133	18.880	11.616	27.771	1.00	35.34

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	ATOM	1087	CB	ASN	A	133	21.662	13.500	27.280	1.00	36.82
	ATOM	1088	CG	ASN	A	133	22.055	14.518	28.327	1.00	42.70
	ATOM	1089	OD1	ASN	A	133	22.192	15.696	27.956	1.00	44.62
	ATOM	1090	ND2	ASN	A	133	22.275	14.088	29.562	1.00	37.77
5	ATOM	1091	N	TRP	A	134	19.546	12.925	29.444	1.00	35.65
	ATOM	1092	CA	TRP	A	134	18.238	12.908	30.127	1.00	36.02
	ATOM	1093	C	TRP	A	134	17.856	14.318	30.510	1.00	36.37
	ATOM	1094	O	TRP	A	134	18.686	15.002	31.095	1.00	37.57
10	ATOM	1095	CB	TRP	A	134	18.363	12.078	31.423	1.00	34.98
	ATOM	1096	CG	TRP	A	134	18.900	10.691	31.221	1.00	35.16
	ATOM	1097	CD1	TRP	A	134	20.214	10.320	31.363	1.00	36.78
	ATOM	1098	CD2	TRP	A	134	18.190	9.511	30.845	1.00	37.83
	ATOM	1099	NE1	TRP	A	134	20.350	8.987	31.103	1.00	33.83
15	ATOM	1100	CE2	TRP	A	134	19.121	8.458	30.802	1.00	34.86
	ATOM	1101	CE3	TRP	A	134	16.836	9.240	30.593	1.00	35.07
	ATOM	1102	CZ2	TRP	A	134	18.770	7.136	30.516	1.00	36.92
	ATOM	1103	CZ3	TRP	A	134	16.498	7.932	30.308	1.00	39.28
	ATOM	1104	CH2	TRP	A	134	17.449	6.905	30.240	1.00	38.59
20	ATOM	1105	N	THR	A	135	16.634	14.807	30.259	1.00	36.82
	ATOM	1106	CA	THR	A	135	16.349	16.149	30.758	1.00	36.51
	ATOM	1107	C	THR	A	135	16.094	16.125	32.270	1.00	37.13
	ATOM	1108	O	THR	A	135	16.234	17.149	32.927	1.00	35.77
	ATOM	1109	CB	THR	A	135	15.214	16.871	30.031	1.00	41.31
	ATOM	1110	OG1	THR	A	135	13.979	16.175	30.224	1.00	39.42
25	ATOM	1111	CG2	THR	A	135	15.461	16.910	28.512	1.00	43.30
	ATOM	1112	N	HIS	A	136	15.650	15.007	32.831	1.00	36.50
	ATOM	1113	CA	HIS	A	136	15.236	14.974	34.227	1.00	37.55
	ATOM	1114	C	HIS	A	136	16.017	13.856	34.948	1.00	36.41
30	ATOM	1115	O	HIS	A	136	15.783	12.717	34.570	1.00	37.39
	ATOM	1116	CB	HIS	A	136	13.731	14.716	34.346	1.00	42.28
	ATOM	1117	CG	HIS	A	136	12.843	15.884	34.044	1.00	45.85
	ATOM	1118	ND1	HIS	A	136	12.928	16.585	32.850	1.00	44.57
	ATOM	1119	CD2	HIS	A	136	11.847	16.467	34.751	1.00	47.41
35	ATOM	1120	CE1	HIS	A	136	12.039	17.564	32.853	1.00	45.33
	ATOM	1121	NE2	HIS	A	136	11.362	17.512	33.987	1.00	49.47
	ATOM	1122	N	ILE	A	137	16.941	14.223	35.827	1.00	35.44
	ATOM	1123	CA	ILE	A	137	17.696	13.165	36.526	1.00	34.42
	ATOM	1124	C	ILE	A	137	17.396	13.291	38.023	1.00	34.06
40	ATOM	1125	O	ILE	A	137	17.573	14.396	38.537	1.00	34.29
	ATOM	1126	CB	ILE	A	137	19.209	13.314	36.268	1.00	33.02
	ATOM	1127	CG1	ILE	A	137	19.527	13.053	34.780	1.00	33.98
	ATOM	1128	CG2	ILE	A	137	19.995	12.315	37.126	1.00	34.85
	ATOM	1129	CD1	ILE	A	137	20.948	13.484	34.427	1.00	35.15
45	ATOM	1130	N	TYR	A	138	16.902	12.217	38.643	1.00	33.90
	ATOM	1131	CA	TYR	A	138	16.497	12.371	40.067	1.00	34.35
	ATOM	1132	C	TYR	A	138	17.618	11.920	40.998	1.00	34.35
	ATOM	1133	O	TYR	A	138	17.925	10.740	40.954	1.00	35.52
	ATOM	1134	CB	TYR	A	138	15.196	11.604	40.319	1.00	35.05
50	ATOM	1135	CG	TYR	A	138	14.075	12.281	39.524	1.00	37.41
	ATOM	1136	CD1	TYR	A	138	13.904	11.924	38.203	1.00	38.75
	ATOM	1137	CD2	TYR	A	138	13.272	13.267	40.084	1.00	40.04
	ATOM	1138	CE1	TYR	A	138	12.922	12.525	37.431	1.00	39.64
	ATOM	1139	CE2	TYR	A	138	12.281	13.870	39.308	1.00	41.81
55	ATOM	1140	CZ	TYR	A	138	12.128	13.492	37.999	1.00	41.16
	ATOM	1141	OH	TYR	A	138	11.171	14.050	37.192	1.00	43.58
	ATOM	1142	N	ILE	A	139	18.255	12.823	41.721	1.00	34.48
	ATOM	1143	CA	ILE	A	139	19.360	12.458	42.607	1.00	35.01
	ATOM	1144	C	ILE	A	139	18.756	12.127	43.996	1.00	34.60
60	ATOM	1145	O	ILE	A	139	18.312	13.089	44.613	1.00	35.20
	ATOM	1146	CB	ILE	A	139	20.353	13.612	42.774	1.00	34.61
	ATOM	1147	CG1	ILE	A	139	20.926	14.098	41.421	1.00	38.01
	ATOM	1148	CG2	ILE	A	139	21.546	13.200	43.637	1.00	37.55
	ATOM	1149	CD1	ILE	A	139	21.487	12.956	40.588	1.00	38.91

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	ATOM	1150	N	CYS	A	140	18.581	10.861	44.301	1.00	35.26
	ATOM	1151	CA	CYS	A	140	17.938	10.511	45.590	1.00	37.11
	ATOM	1152	C	CYS	A	140	18.952	10.174	46.664	1.00	37.66
5	ATOM	1153	O	CYS	A	140	19.865	9.384	46.448	1.00	37.82
	ATOM	1154	CB	CYS	A	140	17.078	9.251	45.411	1.00	42.45
	ATOM	1155	SG	CYS	A	140	15.483	9.689	44.680	1.00	49.17
	ATOM	1156	N	GLU	A	141	18.799	10.796	47.831	1.00	37.14
	ATOM	1157	CA	GLU	A	141	19.664	10.484	48.966	1.00	37.88
10	ATOM	1158	C	GLU	A	141	18.845	9.929	50.125	1.00	36.63
	ATOM	1159	O	GLU	A	141	17.678	9.579	49.925	1.00	35.72
	ATOM	1160	CB	GLU	A	141	20.509	11.709	49.297	1.00	43.42
	ATOM	1161	CG	GLU	A	141	21.392	12.145	48.129	1.00	53.61
	ATOM	1162	CD	GLU	A	141	22.122	13.446	48.352	1.00	58.09
	ATOM	1163	OE1	GLU	A	141	21.544	14.528	48.139	1.00	57.53
15	ATOM	1164	OE2	GLU	A	141	23.308	13.339	48.747	1.00	64.14
	ATOM	1165	N	GLU	A	142	19.445	9.883	51.315	1.00	36.78
	ATOM	1166	CA	GLU	A	142	18.783	9.263	52.479	1.00	36.84
	ATOM	1167	C	GLU	A	142	17.515	9.941	52.907	1.00	35.85
20	ATOM	1168	O	GLU	A	142	16.496	9.267	53.166	1.00	36.59
	ATOM	1169	CB	GLU	A	142	19.780	9.360	53.654	1.00	43.10
	ATOM	1170	CG	GLU	A	142	21.150	8.763	53.466	1.00	54.03
	ATOM	1171	CD	GLU	A	142	22.322	9.696	53.311	1.00	60.55
	ATOM	1172	OE1	GLU	A	142	22.260	10.679	52.543	1.00	59.21
	ATOM	1173	OE2	GLU	A	142	23.401	9.470	53.924	1.00	64.17
25	ATOM	1174	N	ALA	A	143	17.477	11.272	52.922	1.00	34.96
	ATOM	1175	CA	ALA	A	143	16.241	11.960	53.308	1.00	36.52
	ATOM	1176	C	ALA	A	143	15.739	12.999	52.312	1.00	36.98
	ATOM	1177	O	ALA	A	143	15.239	14.019	52.787	1.00	38.22
30	ATOM	1178	CB	ALA	A	143	16.560	12.620	54.652	1.00	34.45
	ATOM	1179	N	SER	A	144	16.163	12.881	51.031	1.00	36.01
	ATOM	1180	CA	SER	A	144	15.754	13.884	50.048	1.00	35.70
	ATOM	1181	C	SER	A	144	15.959	13.477	48.583	1.00	35.68
	ATOM	1182	O	SER	A	144	16.665	12.520	48.259	1.00	34.04
35	ATOM	1183	CB	SER	A	144	16.607	15.158	50.246	1.00	39.92
	ATOM	1184	OG	SER	A	144	17.965	14.791	49.965	1.00	46.64
	ATOM	1185	N	VAL	A	145	15.361	14.287	47.712	1.00	36.14
	ATOM	1186	CA	VAL	A	145	15.576	14.054	46.260	1.00	35.49
	ATOM	1187	C	VAL	A	145	15.546	15.410	45.563	1.00	36.78
40	ATOM	1188	O	VAL	A	145	14.806	16.307	45.979	1.00	34.89
	ATOM	1189	CB	VAL	A	145	14.580	13.058	45.707	1.00	36.75
	ATOM	1190	CG1	VAL	A	145	13.141	13.446	46.028	1.00	36.76
	ATOM	1191	CG2	VAL	A	145	14.730	12.908	44.192	1.00	37.20
	ATOM	1192	N	THR	A	146	16.453	15.595	44.600	1.00	37.23
	ATOM	1193	CA	THR	A	146	16.434	16.814	43.769	1.00	39.11
45	ATOM	1194	C	THR	A	146	16.529	16.390	42.297	1.00	39.36
	ATOM	1195	O	THR	A	146	17.361	15.521	41.981	1.00	39.50
	ATOM	1196	CB	THR	A	146	17.709	17.657	44.040	1.00	43.57
	ATOM	1197	OG1	THR	A	146	17.833	17.886	45.432	1.00	49.29
	ATOM	1198	CG2	THR	A	146	17.686	18.953	43.244	1.00	46.55
50	ATOM	1199	N	VAL	A	147	15.699	16.998	41.454	1.00	39.48
	ATOM	1200	CA	VAL	A	147	15.774	16.719	40.017	1.00	38.72
	ATOM	1201	C	VAL	A	147	16.800	17.682	39.433	1.00	39.04
	ATOM	1202	O	VAL	A	147	16.921	18.842	39.851	1.00	38.28
55	ATOM	1203	CB	VAL	A	147	14.451	16.800	39.268	1.00	40.51
	ATOM	1204	CG1	VAL	A	147	13.871	18.209	39.197	1.00	42.34
	ATOM	1205	CG2	VAL	A	147	14.532	16.183	37.873	1.00	36.37
	ATOM	1206	N	VAL	A	148	17.711	17.103	38.634	1.00	39.16
	ATOM	1207	CA	VAL	A	148	18.685	17.909	37.910	1.00	38.86
	ATOM	1208	C	VAL	A	148	18.569	17.615	36.406	1.00	38.03
60	ATOM	1209	O	VAL	A	148	18.093	16.554	35.994	1.00	38.38
	ATOM	1210	CB	VAL	A	148	20.117	17.663	38.437	1.00	37.94
	ATOM	1211	CG1	VAL	A	148	20.196	17.921	39.948	1.00	37.81
	ATOM	1212	CG2	VAL	A	148	20.543	16.227	38.135	1.00	39.08

	ATOM	1213	N	GLU	A	149	19.105	18.521	35.575	1.00	37.21
	ATOM	1214	CA	GLU	A	149	19.010	18.272	34.118	1.00	37.63
	ATOM	1215	C	GLU	A	149	20.309	17.767	33.517	1.00	36.45
5	ATOM	1216	O	GLU	A	149	21.385	18.214	33.912	1.00	37.57
	ATOM	1217	CB	GLU	A	149	18.519	19.530	33.403	1.00	48.95
	ATOM	1218	CG	GLU	A	149	19.598	20.527	33.046	1.00	53.64
	ATOM	1219	CD	GLU	A	149	19.100	21.544	32.022	1.00	58.00
	ATOM	1220	OE1	GLU	A	149	19.440	22.716	32.229	1.00	55.36
	ATOM	1221	OE2	GLU	A	149	18.363	21.228	31.067	1.00	61.49
10	ATOM	1222	N	GLY	A	150	20.200	16.861	32.559	1.00	37.43
	ATOM	1223	CA	GLY	A	150	21.399	16.289	31.923	1.00	37.28
	ATOM	1224	C	GLY	A	150	21.910	17.392	30.970	1.00	37.55
	ATOM	1225	O	GLY	A	150	21.071	18.016	30.338	1.00	37.62
	ATOM	1226	N	GLN	A	151	23.181	17.714	31.014	1.00	37.21
15	ATOM	1227	CA	GLN	A	151	23.713	18.812	30.210	1.00	36.92
	ATOM	1228	C	GLN	A	151	24.833	18.247	29.331	1.00	37.46
	ATOM	1229	O	GLN	A	151	25.351	17.166	29.610	1.00	35.27
	ATOM	1230	CB	GLN	A	151	24.280	19.937	31.078	1.00	37.56
	ATOM	1231	CG	GLN	A	151	23.177	20.667	31.852	1.00	43.46
20	ATOM	1232	CD	GLN	A	151	23.691	21.877	32.581	1.00	48.78
	ATOM	1233	OE1	GLN	A	151	23.987	22.896	31.946	1.00	49.56
	ATOM	1234	NE2	GLN	A	151	23.820	21.769	33.905	1.00	44.12
	ATOM	1235	N	VAL	A	152	25.173	19.028	28.294	1.00	36.05
	ATOM	1236	CA	VAL	A	152	26.097	18.488	27.284	1.00	36.80
25	ATOM	1237	C	VAL	A	152	27.209	19.494	26.986	1.00	37.21
	ATOM	1238	O	VAL	A	152	26.949	20.667	26.795	1.00	36.72
	ATOM	1239	CB	VAL	A	152	25.385	18.266	25.921	1.00	40.17
	ATOM	1240	CG1	VAL	A	152	26.394	17.345	25.148	1.00	37.05
	ATOM	1241	CG2	VAL	A	152	24.181	17.350	26.088	1.00	42.64
30	ATOM	1242	N	ASP	A	153	28.420	19.032	27.005	1.00	37.01
	ATOM	1243	CA	ASP	A	153	29.712	19.530	26.819	1.00	37.91
	ATOM	1244	C	ASP	A	153	30.452	19.060	25.554	1.00	36.17
	ATOM	1245	O	ASP	A	153	30.094	18.059	24.955	1.00	37.68
	ATOM	1246	CB	ASP	A	153	30.713	19.123	28.066	1.00	30.79
35	ATOM	1247	CG	ASP	A	153	30.890	20.514	28.634	1.00	39.47
	ATOM	1248	OD1	ASP	A	153	30.469	21.441	27.840	1.00	53.60
	ATOM	1249	OD2	ASP	A	153	31.411	20.767	29.695	1.00	41.06
	ATOM	1250	N	TYR	A	154	31.550	19.785	25.263	1.00	36.73
	ATOM	1251	CA	TYR	A	154	32.497	19.232	24.299	1.00	38.06
40	ATOM	1252	C	TYR	A	154	33.107	17.950	24.912	1.00	38.77
	ATOM	1253	O	TYR	A	154	33.386	16.934	24.276	1.00	38.93
	ATOM	1254	CB	TYR	A	154	33.624	20.200	23.920	1.00	38.36
	ATOM	1255	CG	TYR	A	154	34.637	19.489	23.038	1.00	38.72
	ATOM	1256	CD1	TYR	A	154	34.295	19.193	21.714	1.00	39.88
45	ATOM	1257	CD2	TYR	A	154	35.875	19.104	23.514	1.00	39.51
	ATOM	1258	CE1	TYR	A	154	35.184	18.532	20.873	1.00	39.95
	ATOM	1259	CE2	TYR	A	154	36.759	18.454	22.687	1.00	41.22
	ATOM	1260	CZ	TYR	A	154	36.412	18.174	21.376	1.00	41.17
	ATOM	1261	OH	TYR	A	154	37.332	17.516	20.610	1.00	42.16
50	ATOM	1262	N	TYR	A	155	33.319	18.027	26.224	1.00	38.13
	ATOM	1263	CA	TYR	A	155	33.883	16.968	27.018	1.00	38.84
	ATOM	1264	C	TYR	A	155	32.959	15.819	27.350	1.00	37.80
	ATOM	1265	O	TYR	A	155	33.530	14.735	27.543	1.00	37.77
	ATOM	1266	CB	TYR	A	155	34.500	17.518	28.323	1.00	40.03
55	ATOM	1267	CG	TYR	A	155	35.364	18.745	28.031	1.00	43.75
	ATOM	1268	CD1	TYR	A	155	34.854	20.021	28.230	1.00	44.64
	ATOM	1269	CD2	TYR	A	155	36.655	18.604	27.562	1.00	44.86
	ATOM	1270	CE1	TYR	A	155	35.628	21.136	27.950	1.00	46.55
	ATOM	1271	CE2	TYR	A	155	37.440	19.709	27.271	1.00	46.37
60	ATOM	1272	CZ	TYR	A	155	36.920	20.963	27.485	1.00	48.04
	ATOM	1273	OH	TYR	A	155	37.708	22.064	27.230	1.00	50.62
	ATOM	1274	N	GLY	A	156	31.651	16.005	27.491	1.00	36.89
	ATOM	1275	CA	GLY	A	156	30.784	14.894	27.833	1.00	36.27

	ATOM	1276	C	GLY	A	156	29.374	15.297	28.278	1.00	36.29
	ATOM	1277	O	GLY	A	156	28.845	16.351	27.962	1.00	36.73
	ATOM	1278	N	LEU	A	157	28.737	14.367	28.989	1.00	35.47
	ATOM	1279	CA	LEU	A	157	27.410	14.593	29.547	1.00	36.71
5	ATOM	1280	C	LEU	A	157	27.570	14.782	31.061	1.00	36.98
	ATOM	1281	O	LEU	A	157	28.299	14.009	31.703	1.00	37.91
	ATOM	1282	CB	LEU	A	157	26.472	13.404	29.348	1.00	36.06
	ATOM	1283	CG	LEU	A	157	26.409	12.902	27.878	1.00	39.11
	ATOM	1284	CD1	LEU	A	157	25.362	11.777	27.835	1.00	40.34
10	ATOM	1285	CD2	LEU	A	157	25.944	14.021	26.948	1.00	37.66
	ATOM	1286	N	TYR	A	158	26.860	15.773	31.583	1.00	36.59
	ATOM	1287	CA	TYR	A	158	27.043	16.018	33.020	1.00	37.29
	ATOM	1288	C	TYR	A	158	25.778	16.579	33.654	1.00	37.06
	ATOM	1289	O	TYR	A	158	24.813	16.941	32.968	1.00	36.78
15	ATOM	1290	CB	TYR	A	158	28.202	17.007	33.172	1.00	37.24
	ATOM	1291	CG	TYR	A	158	27.948	18.410	32.664	1.00	38.25
	ATOM	1292	CD1	TYR	A	158	27.547	19.427	33.526	1.00	37.59
	ATOM	1293	CD2	TYR	A	158	28.158	18.721	31.322	1.00	38.51
	ATOM	1294	CE1	TYR	A	158	27.355	20.718	33.056	1.00	38.42
20	ATOM	1295	CE2	TYR	A	158	27.955	20.009	30.839	1.00	38.37
	ATOM	1296	CZ	TYR	A	158	27.573	21.006	31.711	1.00	38.61
	ATOM	1297	OH	TYR	A	158	27.359	22.290	31.260	1.00	37.90
	ATOM	1298	N	TYR	A	159	25.799	16.661	34.979	1.00	36.65
	ATOM	1299	CA	TYR	A	159	24.758	17.394	35.694	1.00	37.45
25	ATOM	1300	C	TYR	A	159	25.493	18.169	36.801	1.00	37.16
	ATOM	1301	O	TYR	A	159	26.659	17.920	37.045	1.00	37.16
	ATOM	1302	CB	TYR	A	159	23.638	16.543	36.301	1.00	37.42
	ATOM	1303	CG	TYR	A	159	24.161	15.441	37.222	1.00	37.53
	ATOM	1304	CD1	TYR	A	159	24.429	14.181	36.732	1.00	39.31
30	ATOM	1305	CD2	TYR	A	159	24.352	15.689	38.574	1.00	38.15
	ATOM	1306	CE1	TYR	A	159	24.902	13.169	37.564	1.00	39.89
	ATOM	1307	CE2	TYR	A	159	24.823	14.699	39.407	1.00	38.54
	ATOM	1308	CZ	TYR	A	159	25.101	13.454	38.893	1.00	39.58
	ATOM	1309	OH	TYR	A	159	25.613	12.488	39.741	1.00	40.63
35	ATOM	1310	N	VAL	A	160	24.779	19.122	37.356	1.00	36.88
	ATOM	1311	CA	VAL	A	160	25.251	19.943	38.452	1.00	38.20
	ATOM	1312	C	VAL	A	160	24.277	19.714	39.629	1.00	38.68
	ATOM	1313	O	VAL	A	160	23.078	19.922	39.514	1.00	38.89
	ATOM	1314	CB	VAL	A	160	25.295	21.439	38.094	1.00	41.01
40	ATOM	1315	CG1	VAL	A	160	25.815	22.251	39.288	1.00	39.83
	ATOM	1316	CG2	VAL	A	160	26.254	21.687	36.916	1.00	36.61
	ATOM	1317	N	HIS	A	161	24.818	19.208	40.708	1.00	39.08
	ATOM	1318	CA	HIS	A	161	24.018	18.916	41.919	1.00	39.84
	ATOM	1319	C	HIS	A	161	24.734	19.569	43.095	1.00	39.51
45	ATOM	1320	O	HIS	A	161	25.900	19.316	43.322	1.00	38.92
	ATOM	1321	CB	HIS	A	161	23.939	17.418	42.140	1.00	37.10
	ATOM	1322	CG	HIS	A	161	23.189	16.976	43.377	1.00	36.87
	ATOM	1323	ND1	HIS	A	161	21.908	17.363	43.665	1.00	42.27
	ATOM	1324	CD2	HIS	A	161	23.571	16.163	44.374	1.00	38.66
50	ATOM	1325	CE1	HIS	A	161	21.508	16.811	44.805	1.00	34.42
	ATOM	1326	NE2	HIS	A	161	22.503	16.079	45.262	1.00	40.76
	ATOM	1327	N	GLU	A	162	24.031	20.404	43.832	1.00	41.45
	ATOM	1328	CA	GLU	A	162	24.557	21.115	44.998	1.00	43.07
	ATOM	1329	C	GLU	A	162	25.795	21.928	44.616	1.00	42.85
55	ATOM	1330	O	GLU	A	162	26.806	21.828	45.304	1.00	43.43
	ATOM	1331	CB	GLU	A	162	24.930	20.138	46.121	1.00	46.97
	ATOM	1332	CG	GLU	A	162	23.750	19.235	46.415	1.00	59.55
	ATOM	1333	CD	GLU	A	162	23.494	18.891	47.854	1.00	61.68
	ATOM	1334	OE1	GLU	A	162	22.551	19.508	48.387	1.00	66.02
60	ATOM	1335	OE2	GLU	A	162	24.226	18.027	48.364	1.00	65.49
	ATOM	1336	N	GLY	A	163	25.786	22.518	43.432	1.00	43.79
	ATOM	1337	CA	GLY	A	163	26.930	23.253	42.929	1.00	43.51
	ATOM	1338	C	GLY	A	163	28.023	22.409	42.306	1.00	43.73

	ATOM	1339	O	GLY	A	163	28.958	23.011	41.746	1.00	43.41
	ATOM	1340	N	ILE	A	164	27.986	21.079	42.371	1.00	42.17
	ATOM	1341	CA	ILE	A	164	29.078	20.258	41.896	1.00	41.52
5	ATOM	1342	C	ILE	A	164	28.743	19.687	40.513	1.00	41.11
	ATOM	1343	O	ILE	A	164	27.677	19.110	40.314	1.00	40.21
	ATOM	1344	CB	ILE	A	164	29.442	19.081	42.820	1.00	41.77
	ATOM	1345	CG1	ILE	A	164	29.730	19.597	44.228	1.00	46.60
	ATOM	1346	CG2	ILE	A	164	30.651	18.346	42.258	1.00	43.25
10	ATOM	1347	CD1	ILE	A	164	29.708	18.526	45.303	1.00	50.89
	ATOM	1348	N	ARG	A	165	29.613	20.004	39.561	1.00	40.27
	ATOM	1349	CA	ARG	A	165	29.428	19.508	38.202	1.00	40.37
	ATOM	1350	C	ARG	A	165	29.979	18.082	38.132	1.00	40.18
	ATOM	1351	O	ARG	A	165	31.139	17.889	38.436	1.00	40.87
15	ATOM	1352	CB	ARG	A	165	30.211	20.389	37.205	1.00	43.98
	ATOM	1353	CG	ARG	A	165	30.190	19.775	35.799	1.00	48.81
	ATOM	1354	CD	ARG	A	165	31.056	20.614	34.844	1.00	50.67
	ATOM	1355	NE	ARG	A	165	30.374	21.882	34.644	1.00	54.50
	ATOM	1356	CZ	ARG	A	165	30.245	22.592	33.535	1.00	51.25
20	ATOM	1357	NH1	ARG	A	165	30.788	22.211	32.399	1.00	52.55
	ATOM	1358	NH2	ARG	A	165	29.552	23.727	33.612	1.00	46.13
	ATOM	1359	N	THR	A	166	29.159	17.127	37.747	1.00	38.84
	ATOM	1360	CA	THR	A	166	29.502	15.722	37.710	1.00	37.91
	ATOM	1361	C	THR	A	166	29.318	15.152	36.310	1.00	36.66
25	ATOM	1362	O	THR	A	166	28.167	15.109	35.857	1.00	36.77
	ATOM	1363	CB	THR	A	166	28.621	14.911	38.700	1.00	42.71
	ATOM	1364	OG1	THR	A	166	28.895	15.399	40.034	1.00	43.09
	ATOM	1365	CG2	THR	A	166	28.934	13.427	38.662	1.00	40.93
	ATOM	1366	N	TYR	A	167	30.398	14.733	35.667	1.00	36.29
30	ATOM	1367	CA	TYR	A	167	30.309	14.112	34.342	1.00	36.95
	ATOM	1368	C	TYR	A	167	29.970	12.639	34.466	1.00	37.76
	ATOM	1369	O	TYR	A	167	30.561	11.961	35.335	1.00	39.69
	ATOM	1370	CB	TYR	A	167	31.611	14.231	33.518	1.00	37.91
	ATOM	1371	CG	TYR	A	167	31.797	15.617	32.933	1.00	38.45
35	ATOM	1372	CD1	TYR	A	167	32.311	16.637	33.726	1.00	39.32
	ATOM	1373	CD2	TYR	A	167	31.397	15.937	31.646	1.00	39.69
	ATOM	1374	CE1	TYR	A	167	32.458	17.919	33.243	1.00	38.98
	ATOM	1375	CE2	TYR	A	167	31.535	17.214	31.133	1.00	39.08
	ATOM	1376	CZ	TYR	A	167	32.064	18.201	31.946	1.00	40.35
40	ATOM	1377	OH	TYR	A	167	32.216	19.488	31.494	1.00	39.61
	ATOM	1378	N	PHE	A	168	28.924	12.172	33.821	1.00	37.39
	ATOM	1379	CA	PHE	A	168	28.547	10.772	33.818	1.00	38.28
	ATOM	1380	C	PHE	A	168	28.987	10.058	32.559	1.00	39.29
	ATOM	1381	O	PHE	A	168	28.980	8.825	32.494	1.00	38.30
45	ATOM	1382	CB	PHE	A	168	27.085	10.508	34.167	1.00	38.07
	ATOM	1383	CG	PHE	A	168	26.068	11.226	33.320	1.00	34.93
	ATOM	1384	CD1	PHE	A	168	25.596	10.661	32.153	1.00	36.11
	ATOM	1385	CD2	PHE	A	168	25.609	12.470	33.722	1.00	35.04
	ATOM	1386	CE1	PHE	A	168	24.656	11.337	31.364	1.00	34.93
50	ATOM	1387	CE2	PHE	A	168	24.672	13.140	32.951	1.00	35.38
	ATOM	1388	CZ	PHE	A	168	24.215	12.564	31.799	1.00	30.80
	ATOM	1389	N	VAL	A	169	29.331	10.849	31.524	1.00	39.59
	ATOM	1390	CA	VAL	A	169	30.019	10.310	30.354	1.00	40.03
	ATOM	1391	C	VAL	A	169	31.149	11.322	30.039	1.00	41.32
55	ATOM	1392	O	VAL	A	169	30.904	12.530	30.018	1.00	39.98
	ATOM	1393	CB	VAL	A	169	29.136	10.155	29.112	1.00	39.59
	ATOM	1394	CG1	VAL	A	169	29.988	9.684	27.917	1.00	41.55
	ATOM	1395	CG2	VAL	A	169	28.019	9.107	29.242	1.00	38.14
	ATOM	1396	N	GLN	A	170	32.377	10.844	29.870	1.00	41.92
60	ATOM	1397	CA	GLN	A	170	33.464	11.693	29.396	1.00	42.70
	ATOM	1398	C	GLN	A	170	33.833	11.215	27.990	1.00	43.33
	ATOM	1399	O	GLN	A	170	34.348	10.097	27.861	1.00	43.22
	ATOM	1400	CB	GLN	A	170	34.696	11.627	30.293	1.00	39.48
	ATOM	1401	CG	GLN	A	170	34.448	12.220	31.676	1.00	45.31

	ATOM	1402	CD	GLN	A	170	35.691	12.212	32.542	1.00	46.68
	ATOM	1403	OE1	GLN	A	170	35.649	11.848	33.717	1.00	52.69
	ATOM	1404	NE2	GLN	A	170	36.816	12.618	31.998	1.00	47.58
	ATOM	1405	N	PHE	A	171	33.678	12.076	26.982	1.00	43.04
5	ATOM	1406	CA	PHE	A	171	33.884	11.606	25.629	1.00	44.34
	ATOM	1407	C	PHE	A	171	35.302	11.186	25.340	1.00	45.84
	ATOM	1408	O	PHE	A	171	35.508	10.343	24.446	1.00	45.10
	ATOM	1409	CB	PHE	A	171	33.422	12.612	24.597	1.00	39.68
	ATOM	1410	CG	PHE	A	171	31.961	12.978	24.639	1.00	38.24
10	ATOM	1411	CD1	PHE	A	171	31.016	11.986	24.875	1.00	40.47
	ATOM	1412	CD2	PHE	A	171	31.530	14.269	24.412	1.00	35.50
	ATOM	1413	CE1	PHE	A	171	29.673	12.310	24.905	1.00	37.70
	ATOM	1414	CE2	PHE	A	171	30.187	14.604	24.441	1.00	37.98
	ATOM	1415	CZ	PHE	A	171	29.248	13.621	24.690	1.00	37.99
15	ATOM	1416	N	LYS	A	172	36.287	11.662	26.080	1.00	45.69
	ATOM	1417	CA	LYS	A	172	37.660	11.223	25.889	1.00	47.54
	ATOM	1418	C	LYS	A	172	37.949	9.748	26.138	1.00	48.27
	ATOM	1419	O	LYS	A	172	38.884	9.175	25.570	1.00	48.26
	ATOM	1420	CB	LYS	A	172	38.594	12.102	26.708	1.00	52.42
20	ATOM	1421	CG	LYS	A	172	40.022	12.159	26.201	1.00	57.12
	ATOM	1422	CD	LYS	A	172	40.904	12.971	27.157	1.00	64.24
	ATOM	1423	CE	LYS	A	172	42.362	12.543	27.018	1.00	65.59
	ATOM	1424	NZ	LYS	A	172	43.304	13.691	26.949	1.00	65.87
	ATOM	1425	N	ASP	A	173	37.154	9.132	27.009	1.00	48.25
25	ATOM	1426	CA	ASP	A	173	37.212	7.712	27.287	1.00	49.23
	ATOM	1427	C	ASP	A	173	36.954	6.925	26.007	1.00	49.36
	ATOM	1428	O	ASP	A	173	37.788	6.072	25.701	1.00	49.13
	ATOM	1429	CB	ASP	A	173	36.263	7.269	28.394	1.00	46.27
	ATOM	1430	CG	ASP	A	173	36.627	7.869	29.740	1.00	50.82
30	ATOM	1431	OD1	ASP	A	173	35.740	8.056	30.605	1.00	51.86
	ATOM	1432	OD2	ASP	A	173	37.817	8.158	29.970	1.00	52.02
	ATOM	1433	N	ASP	A	174	35.901	7.144	25.248	1.00	49.89
	ATOM	1434	CA	ASP	A	174	35.671	6.430	24.007	1.00	50.79
	ATOM	1435	C	ASP	A	174	36.647	6.784	22.897	1.00	52.00
35	ATOM	1436	O	ASP	A	174	37.085	5.884	22.165	1.00	51.37
	ATOM	1437	CB	ASP	A	174	34.231	6.582	23.539	1.00	51.65
	ATOM	1438	CG	ASP	A	174	33.276	5.662	24.274	1.00	51.83
	ATOM	1439	OD1	ASP	A	174	33.751	4.664	24.847	1.00	48.40
	ATOM	1440	OD2	ASP	A	174	32.060	5.942	24.269	1.00	52.72
40	ATOM	1441	N	ALA	A	175	37.040	8.053	22.808	1.00	52.36
	ATOM	1442	CA	ALA	A	175	38.024	8.476	21.821	1.00	53.78
	ATOM	1443	C	ALA	A	175	39.362	7.759	21.964	1.00	54.22
	ATOM	1444	O	ALA	A	175	39.999	7.417	20.974	1.00	54.32
	ATOM	1445	CB	ALA	A	175	38.226	9.986	21.910	1.00	51.67
45	ATOM	1446	N	GLU	A	176	39.832	7.508	23.186	1.00	55.55
	ATOM	1447	CA	GLU	A	176	41.120	6.865	23.409	1.00	56.73
	ATOM	1448	C	GLU	A	176	41.015	5.357	23.234	1.00	57.74
	ATOM	1449	O	GLU	A	176	42.025	4.646	23.187	1.00	58.14
	ATOM	1450	CB	GLU	A	176	41.655	7.170	24.806	1.00	56.85
50	ATOM	1451	CG	GLU	A	176	41.910	8.632	25.116	1.00	59.30
	ATOM	1452	CD	GLU	A	176	42.180	8.743	26.537	0.00	99.00
	ATOM	1453	OE1	GLU	A	176	41.740	8.063	27.454	0.00	99.00
	ATOM	1454	OE2	GLU	A	176	43.073	9.574	26.687	0.00	99.00
	ATOM	1455	N	LYS	A	177	39.790	4.852	23.170	1.00	58.44
55	ATOM	1456	CA	LYS	A	177	39.555	3.420	23.024	1.00	59.70
	ATOM	1457	C	LYS	A	177	39.312	3.069	21.561	1.00	60.20
	ATOM	1458	O	LYS	A	177	39.326	1.895	21.198	1.00	60.71
	ATOM	1459	CB	LYS	A	177	38.350	3.040	23.887	1.00	63.58
	ATOM	1460	CG	LYS	A	177	38.054	1.569	24.029	1.00	67.87
60	ATOM	1461	CD	LYS	A	177	37.047	1.277	25.140	1.00	70.02
	ATOM	1462	CE	LYS	A	177	36.872	-0.235	25.242	1.00	73.46
	ATOM	1463	NZ	LYS	A	177	36.221	-0.638	26.517	1.00	75.57
	ATOM	1464	N	TYR	A	178	38.908	4.057	20.758	1.00	60.36

	ATOM	1465	CA	TYR	A	178	38.551	3.798	19.381	1.00	61.69
	ATOM	1466	C	TYR	A	178	39.369	4.563	18.361	1.00	62.23
	ATOM	1467	O	TYR	A	178	39.821	3.923	17.409	1.00	63.37
	ATOM	1468	CB	TYR	A	178	37.057	3.988	19.100	1.00	61.34
5	ATOM	1469	CG	TYR	A	178	36.139	3.197	20.010	1.00	61.39
	ATOM	1470	CD1	TYR	A	178	36.249	1.811	20.081	1.00	62.10
	ATOM	1471	CD2	TYR	A	178	35.189	3.821	20.798	1.00	61.28
	ATOM	1472	CE1	TYR	A	178	35.440	1.072	20.929	1.00	62.32
	ATOM	1473	CE2	TYR	A	178	34.378	3.097	21.651	1.00	62.22
10	ATOM	1474	CZ	TYR	A	178	34.505	1.723	21.707	1.00	62.51
	ATOM	1475	OH	TYR	A	178	33.696	0.989	22.540	1.00	62.15
	ATOM	1476	N	SER	A	179	39.573	5.858	18.525	1.00	62.95
	ATOM	1477	CA	SER	A	179	40.159	6.703	17.498	1.00	64.19
	ATOM	1478	C	SER	A	179	41.662	6.923	17.631	1.00	64.98
15	ATOM	1479	O	SER	A	179	42.279	6.550	18.630	1.00	64.79
	ATOM	1480	CB	SER	A	179	39.470	8.077	17.505	1.00	65.34
	ATOM	1481	OG	SER	A	179	39.982	8.923	16.491	1.00	69.64
	ATOM	1482	N	LYS	A	180	42.254	7.552	16.609	1.00	65.75
	ATOM	1483	CA	LYS	A	180	43.672	7.876	16.658	1.00	66.93
20	ATOM	1484	C	LYS	A	180	43.886	9.316	17.107	1.00	67.25
	ATOM	1485	O	LYS	A	180	44.806	9.591	17.887	1.00	67.85
	ATOM	1486	CB	LYS	A	180	44.431	7.615	15.360	1.00	69.83
	ATOM	1487	CG	LYS	A	180	45.938	7.673	15.581	1.00	73.65
	ATOM	1488	CD	LYS	A	180	46.681	8.326	14.427	1.00	76.04
25	ATOM	1489	CE	LYS	A	180	48.016	8.889	14.887	1.00	75.99
	ATOM	1490	NZ	LYS	A	180	47.829	10.056	15.790	1.00	78.28
	ATOM	1491	N	ASN	A	181	43.017	10.216	16.652	1.00	66.93
	ATOM	1492	CA	ASN	A	181	43.126	11.609	17.113	1.00	66.52
	ATOM	1493	C	ASN	A	181	42.128	11.842	18.240	1.00	65.58
30	ATOM	1494	O	ASN	A	181	41.133	11.131	18.348	1.00	65.86
	ATOM	1495	CB	ASN	A	181	43.174	12.454	16.113	0.00	99.00
	ATOM	1496	CG	ASN	A	181	44.528	12.902	15.624	0.00	99.00
	ATOM	1497	OD1	ASN	A	181	45.545	12.248	15.833	0.00	99.00
	ATOM	1498	ND2	ASN	A	181	44.525	14.056	14.935	0.00	99.00
35	ATOM	1499	N	LYS	A	182	42.432	12.756	19.155	1.00	65.06
	ATOM	1500	CA	LYS	A	182	41.483	13.086	20.232	1.00	62.47
	ATOM	1501	C	LYS	A	182	40.755	14.370	19.855	1.00	60.44
	ATOM	1502	O	LYS	A	182	40.951	15.405	20.491	1.00	60.89
	ATOM	1503	CB	LYS	A	182	42.257	13.224	21.544	1.00	68.03
40	ATOM	1504	CG	LYS	A	182	41.462	13.626	22.774	1.00	70.69
	ATOM	1505	CD	LYS	A	182	42.223	14.606	23.651	1.00	73.12
	ATOM	1506	CE	LYS	A	182	41.360	15.246	24.718	1.00	73.28
	ATOM	1507	NZ	LYS	A	182	40.729	16.534	24.325	1.00	74.63
	ATOM	1508	N	VAL	A	183	40.007	14.401	18.761	1.00	58.04
45	ATOM	1509	CA	VAL	A	183	39.240	15.559	18.324	1.00	55.16
	ATOM	1510	C	VAL	A	183	37.899	15.073	17.781	1.00	52.42
	ATOM	1511	O	VAL	A	183	37.902	14.220	16.898	1.00	52.43
	ATOM	1512	CB	VAL	A	183	39.936	16.462	17.302	1.00	58.84
	ATOM	1513	CG1	VAL	A	183	38.965	17.219	16.395	1.00	61.12
50	ATOM	1514	CG2	VAL	A	183	40.809	17.504	18.010	1.00	60.87
	ATOM	1515	N	TRP	A	184	36.785	15.581	18.302	1.00	49.48
	ATOM	1516	CA	TRP	A	184	35.495	15.042	17.878	1.00	45.59
	ATOM	1517	C	TRP	A	184	34.490	16.159	17.706	1.00	44.01
	ATOM	1518	O	TRP	A	184	34.791	17.353	17.913	1.00	42.88
55	ATOM	1519	CB	TRP	A	184	35.049	13.926	18.839	1.00	42.62
	ATOM	1520	CG	TRP	A	184	35.075	14.460	20.253	1.00	39.47
	ATOM	1521	CD1	TRP	A	184	34.123	15.236	20.830	1.00	37.50
	ATOM	1522	CD2	TRP	A	184	36.109	14.271	21.216	1.00	41.84
	ATOM	1523	NE1	TRP	A	184	34.491	15.541	22.123	1.00	36.00
60	ATOM	1524	CE2	TRP	A	184	35.717	14.963	22.380	1.00	39.37
	ATOM	1525	CE3	TRP	A	184	37.328	13.587	21.201	1.00	39.30
	ATOM	1526	CZ2	TRP	A	184	36.504	14.983	23.529	1.00	41.08
	ATOM	1527	CZ3	TRP	A	184	38.105	13.599	22.341	1.00	41.95

	ATOM	1528	CH2	TRP	A	184	37.692	14.293	23.486	1.00	42.37
	ATOM	1529	N	GLU	A	185	33.292	15.809	17.270	1.00	42.34
	ATOM	1530	CA	GLU	A	185	32.211	16.770	17.099	1.00	42.70
	ATOM	1531	C	GLU	A	185	30.950	16.204	17.765	1.00	43.74
5	ATOM	1532	O	GLU	A	185	30.589	15.062	17.506	1.00	43.14
	ATOM	1533	CB	GLU	A	185	31.903	17.074	15.635	1.00	42.03
	ATOM	1534	CG	GLU	A	185	33.023	17.900	14.999	1.00	38.91
	ATOM	1535	CD	GLU	A	185	32.851	18.134	13.528	1.00	42.12
10	ATOM	1536	OE1	GLU	A	185	31.953	17.527	12.910	1.00	40.53
	ATOM	1537	OE2	GLU	A	185	33.641	18.955	13.015	1.00	39.53
	ATOM	1538	N	VAL	A	186	30.374	17.021	18.653	1.00	43.76
	ATOM	1539	CA	VAL	A	186	29.211	16.563	19.400	1.00	43.51
	ATOM	1540	C	VAL	A	186	27.943	17.165	18.791	1.00	45.37
	ATOM	1541	O	VAL	A	186	27.804	18.379	18.647	1.00	43.51
15	ATOM	1542	CB	VAL	A	186	29.339	17.008	20.872	1.00	41.67
	ATOM	1543	CG1	VAL	A	186	28.159	16.494	21.688	1.00	41.68
	ATOM	1544	CG2	VAL	A	186	30.697	16.596	21.452	1.00	34.89
	ATOM	1545	N	HIS	A	187	27.012	16.272	18.454	1.00	46.62
	ATOM	1546	CA	HIS	A	187	25.679	16.656	18.003	1.00	50.05
20	ATOM	1547	C	HIS	A	187	24.620	16.257	19.023	1.00	52.23
	ATOM	1548	O	HIS	A	187	24.447	15.055	19.262	1.00	52.60
	ATOM	1549	CB	HIS	A	187	25.329	15.949	16.672	1.00	51.22
	ATOM	1550	CG	HIS	A	187	26.356	16.159	15.600	1.00	53.27
	ATOM	1551	ND1	HIS	A	187	26.135	16.916	14.467	1.00	55.72
25	ATOM	1552	CD2	HIS	A	187	27.633	15.710	15.495	1.00	54.05
	ATOM	1553	CE1	HIS	A	187	27.216	16.925	13.713	1.00	49.24
	ATOM	1554	NE2	HIS	A	187	28.134	16.205	14.329	1.00	53.78
	ATOM	1555	N	ALA	A	188	23.836	17.199	19.524	1.00	54.61
	ATOM	1556	CA	ALA	A	188	22.883	16.882	20.591	1.00	57.68
30	ATOM	1557	C	ALA	A	188	21.502	17.477	20.393	1.00	59.90
	ATOM	1558	O	ALA	A	188	20.747	17.673	21.356	1.00	60.86
	ATOM	1559	CB	ALA	A	188	23.501	17.291	21.929	1.00	57.50
	ATOM	1560	N	GLY	A	189	21.107	17.773	19.155	1.00	61.42
35	ATOM	1561	CA	GLY	A	189	19.809	18.381	18.867	1.00	62.45
	ATOM	1562	C	GLY	A	189	19.862	19.892	18.710	1.00	62.76
	ATOM	1563	O	GLY	A	189	18.863	20.613	18.809	1.00	63.40
	ATOM	1564	N	GLY	A	190	21.051	20.429	18.448	1.00	62.37
	ATOM	1565	CA	GLY	A	190	21.211	21.883	18.338	1.00	60.60
	ATOM	1566	C	GLY	A	190	22.551	22.159	17.660	1.00	58.62
40	ATOM	1567	O	GLY	A	190	23.029	21.274	16.958	1.00	58.39
	ATOM	1568	N	GLN	A	191	23.173	23.285	17.983	1.00	56.77
	ATOM	1569	CA	GLN	A	191	24.466	23.554	17.336	1.00	54.69
	ATOM	1570	C	GLN	A	191	25.462	22.451	17.687	1.00	52.57
	ATOM	1571	O	GLN	A	191	25.599	22.082	18.858	1.00	52.69
45	ATOM	1572	CB	GLN	A	191	24.972	24.927	17.760	1.00	58.35
	ATOM	1573	CG	GLN	A	191	26.437	25.200	17.502	1.00	62.97
	ATOM	1574	CD	GLN	A	191	26.166	26.948	17.561	0.00	99.00
	ATOM	1575	OE1	GLN	A	191	25.459	27.683	16.891	0.00	99.00
	ATOM	1576	NE2	GLN	A	191	27.070	27.403	18.451	0.00	99.00
50	ATOM	1577	N	VAL	A	192	26.162	21.943	16.684	1.00	49.07
	ATOM	1578	CA	VAL	A	192	27.264	21.012	16.898	1.00	45.59
	ATOM	1579	C	VAL	A	192	28.237	21.647	17.875	1.00	44.47
	ATOM	1580	O	VAL	A	192	28.473	22.853	17.803	1.00	45.15
	ATOM	1581	CB	VAL	A	192	27.960	20.717	15.544	1.00	42.50
55	ATOM	1582	CG1	VAL	A	192	29.047	19.665	15.684	1.00	39.90
	ATOM	1583	CG2	VAL	A	192	26.874	20.237	14.584	1.00	40.84
	ATOM	1584	N	ILE	A	193	28.831	20.882	18.775	1.00	41.81
	ATOM	1585	CA	ILE	A	193	29.875	21.406	19.636	1.00	39.71
	ATOM	1586	C	ILE	A	193	31.246	21.009	19.127	1.00	40.00
60	ATOM	1587	O	ILE	A	193	31.569	19.822	19.009	1.00	40.12
	ATOM	1588	CB	ILE	A	193	29.715	20.868	21.104	1.00	36.14
	ATOM	1589	CG1	ILE	A	193	28.303	21.218	21.573	1.00	38.63
	ATOM	1590	CG2	ILE	A	193	30.765	21.585	21.957	1.00	38.85

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	ATOM	1591	CD1	ILE	A	193	27.916	20.591	22.922	1.00	41.29
	ATOM	1592	N	LEU	A	194	32.075	22.008	18.852	1.00	39.67
	ATOM	1593	CA	LEU	A	194	33.436	21.783	18.388	1.00	40.23
	ATOM	1594	C	LEU	A	194	34.455	21.944	19.486	1.00	40.97
5	ATOM	1595	O	LEU	A	194	34.136	22.489	20.557	1.00	40.07
	ATOM	1596	CB	LEU	A	194	33.741	22.794	17.252	1.00	38.19
	ATOM	1597	CG	LEU	A	194	32.736	22.764	16.101	1.00	42.91
	ATOM	1598	CD1	LEU	A	194	33.203	23.702	14.980	1.00	42.33
	ATOM	1599	CD2	LEU	A	194	32.593	21.362	15.514	1.00	41.05
10	ATOM	1600	N	CYS	A	195	35.658	21.430	19.269	1.00	41.29
	ATOM	1601	CA	CYS	A	195	36.711	21.575	20.273	1.00	43.15
	ATOM	1602	C	CYS	A	195	36.956	23.045	20.562	1.00	45.32
	ATOM	1603	O	CYS	A	195	37.083	23.872	19.671	1.00	44.47
	ATOM	1604	CB	CYS	A	195	37.981	20.893	19.785	1.00	44.75
15	ATOM	1605	SG	CYS	A	195	39.358	21.057	20.920	1.00	43.19
	ATOM	1606	N	PRO	A	196	36.918	23.423	21.847	1.00	46.44
	ATOM	1607	CA	PRO	A	196	36.978	24.814	22.245	1.00	47.49
	ATOM	1608	C	PRO	A	196	38.376	25.335	22.514	1.00	48.05
	ATOM	1609	O	PRO	A	196	38.575	26.531	22.759	1.00	49.91
20	ATOM	1610	CB	PRO	A	196	36.123	24.820	23.515	1.00	48.09
	ATOM	1611	CG	PRO	A	196	36.293	23.449	24.079	1.00	47.48
	ATOM	1612	CD	PRO	A	196	36.834	22.513	23.018	1.00	47.09
	ATOM	1613	N	THR	A	197	39.365	24.477	22.488	1.00	48.20
	ATOM	1614	CA	THR	A	197	40.753	24.821	22.766	1.00	49.51
25	ATOM	1615	C	THR	A	197	41.610	24.697	21.491	1.00	48.70
	ATOM	1616	O	THR	A	197	41.132	24.143	20.508	1.00	47.51
	ATOM	1617	CB	THR	A	197	41.337	23.819	23.789	1.00	54.19
	ATOM	1618	OG1	THR	A	197	42.063	22.755	23.133	1.00	60.20
	ATOM	1619	CG2	THR	A	197	40.249	23.146	24.620	1.00	60.00
30	ATOM	1620	N	SER	A	198	42.874	25.104	21.600	1.00	48.43
	ATOM	1621	CA	SER	A	198	43.755	25.011	20.443	1.00	49.41
	ATOM	1622	C	SER	A	198	44.106	23.572	20.088	1.00	51.13
	ATOM	1623	O	SER	A	198	44.340	22.748	20.974	1.00	50.32
	ATOM	1624	CB	SER	A	198	45.022	25.837	20.600	1.00	41.67
35	ATOM	1625	OG	SER	A	198	44.689	27.176	20.863	1.00	42.21
	ATOM	1626	N	VAL	A	199	44.135	23.321	18.783	1.00	51.78
	ATOM	1627	CA	VAL	A	199	44.448	22.018	18.210	1.00	54.21
	ATOM	1628	C	VAL	A	199	45.846	22.063	17.593	1.00	55.85
	ATOM	1629	O	VAL	A	199	46.229	23.043	16.958	1.00	55.32
40	ATOM	1630	CB	VAL	A	199	43.415	21.673	17.105	1.00	55.83
	ATOM	1631	CG1	VAL	A	199	43.848	20.450	16.311	1.00	58.48
	ATOM	1632	CG2	VAL	A	199	42.081	21.363	17.794	1.00	58.90
	ATOM	1633	N	PHE	A	200	46.643	21.031	17.823	1.00	57.80
	ATOM	1634	CA	PHE	A	200	48.033	20.977	17.458	1.00	60.84
45	ATOM	1635	C	PHE	A	200	48.501	19.863	16.538	1.00	63.34
	ATOM	1636	O	PHE	A	200	47.988	18.771	16.373	1.00	63.71
	ATOM	1637	CB	PHE	A	200	48.976	20.962	18.695	1.00	56.48
	ATOM	1638	CG	PHE	A	200	49.009	22.350	19.286	1.00	51.93
	ATOM	1639	CD1	PHE	A	200	49.867	23.304	18.779	1.00	50.53
50	ATOM	1640	CD2	PHE	A	200	48.118	22.686	20.298	1.00	52.06
	ATOM	1641	CE1	PHE	A	200	49.844	24.596	19.289	1.00	48.79
	ATOM	1642	CE2	PHE	A	200	48.104	23.972	20.813	1.00	46.67
	ATOM	1643	CZ	PHE	A	200	48.952	24.921	20.283	1.00	48.73
	ATOM	1644	N	SER	A	201	49.612	20.201	15.906	1.00	65.54
55	ATOM	1645	CA	SER	A	201	50.520	19.367	15.151	1.00	67.49
	ATOM	1646	C	SER	A	201	50.543	17.927	15.652	1.00	68.56
	ATOM	1647	O	SER	A	201	50.873	17.710	16.841	1.00	69.46
	ATOM	1648	CB	SER	A	201	51.928	19.984	15.374	1.00	69.06
	ATOM	1649	OG	SER	A	201	51.799	21.376	15.666	1.00	64.56
60	ATOM	1650	OT	SER	A	201	50.201	17.025	14.856	1.00	71.71
	ATOM	1651	OWO	WAT	W	1	16.850	8.350	41.749	1.00	33.70
	ATOM	1652	OWO	WAT	W	2	14.700	3.706	36.739	1.00	34.70
	ATOM	1653	OWO	WAT	W	3	23.512	-21.581	45.725	1.00	35.04

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	ATOM	1717	OWO	WAT	W	67	16.159	-6.928	39.274	1.00	50.79
	ATOM	1718	OWO	WAT	W	68	18.759	17.803	28.696	1.00	50.80
	ATOM	1719	OWO	WAT	W	69	13.821	14.472	25.933	1.00	52.01
	ATOM	1720	OWO	WAT	W	70	5.992	2.145	50.465	1.00	52.52
5	ATOM	1721	OWO	WAT	W	71	22.450	0.866	42.331	1.00	52.86
	ATOM	1722	OWO	WAT	W	72	37.480	14.455	29.856	1.00	52.16
	ATOM	1723	OWO	WAT	W	73	7.914	14.799	34.609	1.00	52.26
	ATOM	1724	OWO	WAT	W	74	33.074	14.728	12.928	1.00	52.80
	ATOM	1725	OWO	WAT	W	75	-2.139	5.177	35.817	1.00	53.07
10	ATOM	1726	OWO	WAT	W	76	8.849	6.339	29.567	1.00	53.08
	ATOM	1727	OWO	WAT	W	77	2.499	9.596	40.507	1.00	53.22
	ATOM	1728	OWO	WAT	W	78	8.453	-4.313	50.928	1.00	53.22
	ATOM	1729	OWO	WAT	W	79	13.988	-16.279	37.477	1.00	54.52
	ATOM	1730	OWO	WAT	W	80	29.311	23.613	25.169	1.00	53.94
15	ATOM	1731	OWO	WAT	W	81	10.698	17.607	37.556	1.00	53.87
	ATOM	1732	OWO	WAT	W	82	10.533	-28.803	42.420	1.00	54.34
	ATOM	1733	OWO	WAT	W	83	1.674	-0.659	35.990	1.00	54.11
	ATOM	1734	OWO	WAT	W	84	13.238	5.649	29.129	1.00	54.35
	ATOM	1735	OWO	WAT	W	85	23.172	23.184	42.047	1.00	53.98
20	ATOM	1736	OWO	WAT	W	86	25.591	-14.157	41.467	1.00	54.33
	ATOM	1737	OWO	WAT	W	87	39.505	4.678	27.285	1.00	55.10
	ATOM	1738	OWO	WAT	W	88	33.071	24.177	22.504	1.00	53.92
	ATOM	1739	OWO	WAT	W	89	2.865	-14.306	47.361	1.00	55.09
	ATOM	1740	OWO	WAT	W	90	10.824	5.199	27.990	1.00	54.87
25	ATOM	1741	OWO	WAT	W	91	13.268	-18.762	37.013	1.00	55.07
	ATOM	1742	OWO	WAT	W	92	19.672	23.135	34.883	1.00	56.03
	ATOM	1743	OWO	WAT	W	93	3.899	3.408	32.498	1.00	56.24
	ATOM	1744	OWO	WAT	W	94	17.326	5.781	50.106	1.00	56.35
	ATOM	1745	OWO	WAT	W	95	46.420	28.753	20.001	1.00	56.50
30	ATOM	1746	OWO	WAT	W	96	18.033	-25.950	38.021	1.00	56.78
	ATOM	1747	OWO	WAT	W	97	16.668	11.173	20.729	1.00	57.28
	ATOM	1748	OWO	WAT	W	98	-0.327	-1.130	37.865	1.00	56.31
	ATOM	1749	OWO	WAT	W	99	13.791	-29.887	42.473	1.00	56.28
	ATOM	1750	OWO	WAT	W	100	14.138	-6.120	36.256	1.00	56.78
35	ATOM	1751	OWO	WAT	W	101	-0.503	-1.004	43.200	1.00	56.68
	ATOM	1752	OWO	WAT	W	102	7.034	2.268	29.920	1.00	57.78
	ATOM	1753	OWO	WAT	W	103	39.612	16.983	21.840	1.00	57.56
	ATOM	1754	OWO	WAT	W	104	12.322	-7.683	34.772	1.00	57.82
	ATOM	1755	OWO	WAT	W	105	21.186	21.778	39.197	1.00	58.10
40	ATOM	1756	OWO	WAT	W	106	25.213	27.127	14.493	1.00	58.04
	ATOM	1757	OWO	WAT	W	107	37.189	5.450	11.613	1.00	58.31
	ATOM	1758	OWO	WAT	W	108	25.799	-17.600	47.916	1.00	58.58
	ATOM	1759	OWO	WAT	W	109	25.505	0.503	36.518	1.00	57.70
	ATOM	1760	OWO	WAT	W	110	21.154	19.292	24.315	1.00	58.80
45	ATOM	1761	OWO	WAT	W	111	23.932	23.123	29.269	1.00	58.45
	ATOM	1762	OWO	WAT	W	112	30.025	16.034	12.701	1.00	58.92
	ATOM	1763	OWO	WAT	W	113	5.440	-12.369	36.445	1.00	60.00
	ATOM	1764	OWO	WAT	W	114	45.949	18.908	19.720	1.00	59.22
	ATOM	1765	OWO	WAT	W	115	3.882	16.171	43.893	1.00	59.38
50	ATOM	1766	OWO	WAT	W	116	26.040	-17.629	41.513	1.00	58.92
	ATOM	1767	OWO	WAT	W	117	13.942	-10.256	37.298	1.00	60.39
	ATOM	1768	OWO	WAT	W	118	7.840	10.062	31.734	1.00	60.14
	ATOM	1769	OWO	WAT	W	119	-1.860	-20.559	43.212	1.00	60.45
	ATOM	1770	OWO	WAT	W	120	18.311	16.851	47.879	1.00	60.32
55	ATOM	1771	OWO	WAT	W	121	38.093	15.693	26.658	1.00	61.27
	ATOM	1772	OWO	WAT	W	122	7.557	-26.418	44.769	1.00	61.39
	ATOM	1773	OWO	WAT	W	123	17.200	-4.612	32.783	1.00	60.41
	ATOM	1774	OWO	WAT	W	124	33.055	9.791	13.378	1.00	61.34
	ATOM	1775	OWO	WAT	W	125	29.579	10.149	37.422	1.00	60.84
60	ATOM	1776	OWO	WAT	W	126	26.196	13.297	42.367	1.00	60.80
	ATOM	1777	OWO	WAT	W	127	23.556	-4.737	42.642	1.00	61.18
	ATOM	1778	OWO	WAT	W	128	10.687	-3.375	35.374	1.00	61.88
	ATOM	1779	OWO	WAT	W	129	13.030	-13.947	38.339	1.00	62.52

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	ATOM	1780	OWO	WAT	W	130	9.747	-0.992	36.212	1.00	59.32
	ATOM	1781	OWO	WAT	W	131	24.814	-11.997	45.661	1.00	62.19
	ATOM	1782	OWO	WAT	W	132	23.200	4.574	23.546	1.00	61.90
	ATOM	1783	OWO	WAT	W	133	24.938	30.370	17.496	1.00	62.23
5	ATOM	1784	OWO	WAT	W	134	35.459	1.260	16.603	1.00	62.66
	ATOM	1785	OWO	WAT	W	135	24.178	20.068	20.090	1.00	61.73
	ATOM	1786	OWO	WAT	W	136	40.127	0.350	18.771	1.00	62.44
	ATOM	1787	OWO	WAT	W	137	19.279	14.663	46.778	1.00	63.59
	ATOM	1788	OWO	WAT	W	138	20.090	20.354	46.023	1.00	62.81
10	ATOM	1789	OWO	WAT	W	139	15.250	18.974	46.516	1.00	63.68
	ATOM	1790	OWO	WAT	W	140	21.267	-25.030	39.386	1.00	63.31
	ATOM	1791	OWO	WAT	W	141	26.107	2.756	33.033	1.00	63.89
	ATOM	1792	OWO	WAT	W	142	13.216	16.259	48.398	1.00	64.51
	ATOM	1793	OWO	WAT	W	143	23.474	19.596	51.112	1.00	65.45
15	ATOM	1794	OWO	WAT	W	144	6.778	10.141	28.981	1.00	64.57
	ATOM	1795	OWO	WAT	W	145	23.613	15.848	49.685	1.00	64.50
	ATOM	1796	OWO	WAT	W	146	21.834	-6.518	36.556	1.00	65.24
	ATOM	1797	OWO	WAT	W	147	10.139	-10.444	36.806	1.00	65.85
	ATOM	1798	OWO	WAT	W	148	32.489	10.232	33.677	1.00	64.60
20	ATOM	1799	OWO	WAT	W	149	31.655	6.263	27.510	1.00	64.29
	ATOM	1800	OWO	WAT	W	150	4.585	-20.934	39.031	1.00	66.94
	ATOM	1801	OWO	WAT	W	151	38.484	11.674	18.085	1.00	65.84
	ATOM	1802	OWO	WAT	W	152	42.438	8.992	21.219	1.00	65.71
	ATOM	1803	OWO	WAT	W	153	33.971	24.173	27.259	1.00	66.15
25	ATOM	1804	OWO	WAT	W	154	24.597	-9.268	45.286	1.00	67.06
	ATOM	1805	OWO	WAT	W	155	-2.112	-26.008	50.039	1.00	66.08
	ATOM	1806	OWO	WAT	W	156	9.030	-32.481	39.896	1.00	66.14
	ATOM	1807	OWO	WAT	W	157	-3.216	-18.835	45.004	1.00	67.94
	ATOM	1808	OWO	WAT	W	158	-3.398	4.020	40.260	1.00	65.32
30	ATOM	1809	OWO	WAT	W	159	25.878	24.231	20.622	1.00	68.10
	ATOM	1810	OWO	WAT	W	160	27.187	4.546	24.805	1.00	67.75
	ATOM	1811	OWO	WAT	W	161	24.071	24.303	35.784	1.00	67.51
	ATOM	1812	OWO	WAT	W	162	7.746	17.585	52.663	1.00	70.19
	ATOM	1813	OWO	WAT	W	163	19.301	4.980	47.873	1.00	68.23
35	ATOM	1814	OWO	WAT	W	164	10.439	-4.135	32.539	1.00	65.45
	ATOM	1815	OWO	WAT	W	165	23.798	-0.930	41.113	1.00	68.64
	ATOM	1816	OWO	WAT	W	166	2.464	5.318	30.549	1.00	65.77
	ATOM	1817	OWO	WAT	W	167	9.665	-14.876	35.700	1.00	65.21
	ATOM	1818	OWO	WAT	W	168	1.759	10.431	44.227	1.00	69.25
40	ATOM	1819	OWO	WAT	W	169	20.960	4.214	26.258	1.00	69.97
	ATOM	1820	OWO	WAT	W	170	28.769	24.807	27.878	1.00	67.86
	ATOM	1821	OWO	WAT	W	171	30.212	14.473	8.293	1.00	69.23
	ATOM	1822	OWO	WAT	W	172	20.178	0.312	50.589	1.00	70.29
	ATOM	1823	OWO	WAT	W	173	19.736	6.852	23.117	1.00	70.72
45	ATOM	1824	OWO	WAT	W	174	8.978	16.807	50.514	1.00	70.10
	ATOM	1825	OWO	WAT	W	175	25.144	-1.759	34.429	1.00	71.96
	ATOM	1826	OWO	WAT	W	176	26.946	25.298	35.563	1.00	68.69
	ATOM	1827	OWO	WAT	W	177	44.918	5.619	13.054	1.00	70.16
	ATOM	1828	OWO	WAT	W	178	22.370	24.094	38.170	1.00	71.66
50	ATOM	1829	OWO	WAT	W	179	-0.624	10.187	33.201	1.00	72.23
	ATOM	1830	OWO	WAT	W	180	11.015	17.856	47.520	1.00	71.42
	ATOM	1831	OWO	WAT	W	181	7.766	0.898	52.950	1.00	71.64
	ATOM	1832	OWO	WAT	W	182	3.469	-28.368	52.511	1.00	70.10

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Claims

- 5 1. A crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, comprising residues vital for transcriptional and replicational activities of said protein.
2. An E2NT dimer protein according to Claim 1 wherein the residues lie on
10 opposite sides of an N-terminal domain.
3. An E2NT dimer protein according to either preceding claim wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the
15 dimer.
4. An E2NT dimer according to Claim 3 comprising three clusters.
5. An E2NT dimer according to either of Claims 3 or 4 wherein a first cluster of
20 vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.
6. An E2NT dimer according to any one of Claims 3-5 wherein a second cluster
25 of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.
7. An E2NT dimer according to any one of Claims 3-6 wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the
30 following residues Pro106, Lys111, Phe168, Trp134.

8. An E2NT dimer according to any preceding claim further comprising residues associated with transactivation and/or replication properties of E2.
9. An E2NT dimer according to Claim 8 wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.
10. Use of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein according to any preceding claim or homologue thereof in mapping mutations onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.
11. Use according to Claim 10 in rationalised antiviral drug design.
12. An *in vitro* method for identifying and/or selecting a candidate therapeutic agent, the method comprising determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2.
13. Use of the method according to Claim 12 in identifying and/or selecting an antiviral candidate therapeutic agent.
14. Use according to Claim 13 wherein identification/selection of the candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.
15. Use of an E2NT dimerisation inhibitor for the preparation of a medicament for treatment of conditions that arise as a result of HPV infection.
16. Use according to Claim 15 for the treatment of warts, proliferative skin lesions and/or cervical cancer.

17. A method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of an HPV infection comprising taking a sample from said patient and measuring E2NT interactions and/or DNA loop
5 formation.
18. Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to any one of Claims 1-9 as a target site for interaction with putative antiviral agents and/or for
10 measuring efficacy of said agents.
19. A method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal
15 structure using X-ray diffraction.
20. A method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.
- 20 21. A method of claim 19 or claim 20 wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.
22. A method of any of claims 19 to 21, wherein the crystal structure comprises
25 the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.
23. A method of any of claims 19 to 22, wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.
30
24. A computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises or a

three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

5

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3;

10

(b) a working memory for storing instructions for processing said machine-readable data;

15

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

20

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

25

25. The computer according to claim 24, wherein said three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

30

26. A computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

- (a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;
- 5 (b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;
- (c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);
- 10 (d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b)
- 15 into structure coordinates; and
- (e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.
- 20 27. A crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3 or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation
- 25 from the backbone atoms of said amino acids of not more than 1.5Å.
28. The crystallized molecule or molecular complex according to claim 27, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue
- 30 has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

29. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

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30. The machine-readable data storage medium according to claim 7, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

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31. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

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32. A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to claim 27 or claim 28 comprising the steps of:

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- a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and
- b. analysing the results of said fitting operation to quantify the association
- 5 between the chemical entity and the dimerisation surface.

33. A drug or therapeutic agent identified, assessed or selected using a crystallised molecular complex of an E2NT protein or its crystal structure or using a complex of any of claims 1 to 9, a method of claim 12, a use of any of claims 13,

10 claim 14 or 18. a method of any of claims 20 to 24 or 32 or a product of any of claims 25 to 31.

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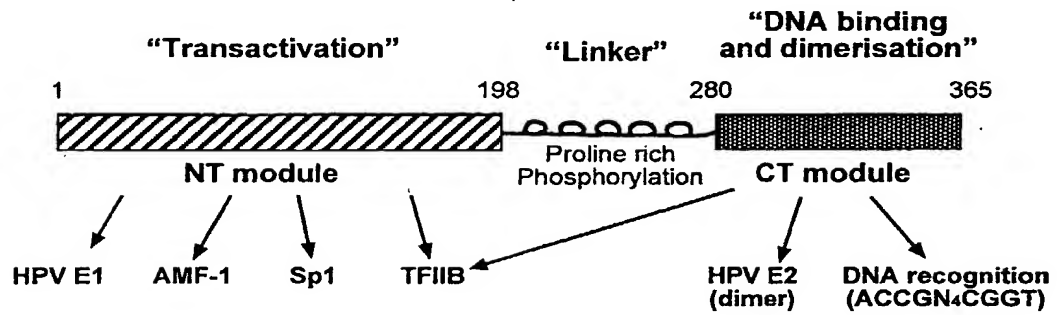
(57) Abstract: A crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, that comprises residues vital for viral transcription and/or replication. The invention also provides for the use of the dimer protein and interactions at its dimerisation surface in rationalised antiviral drug design.



WO 01/21645 A2

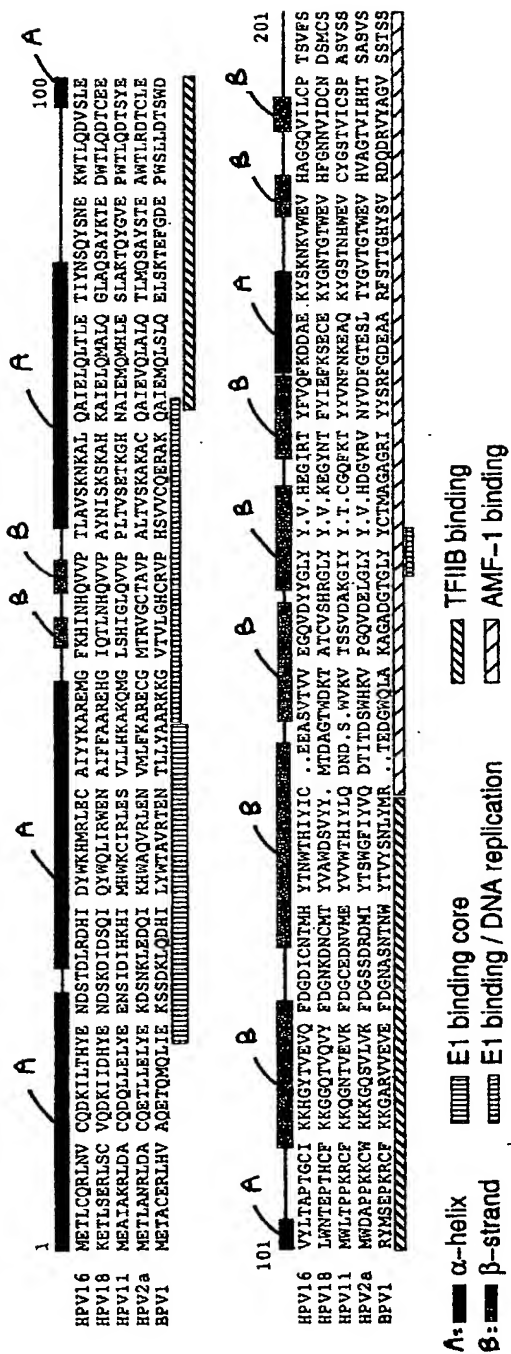
FIG. 1. A

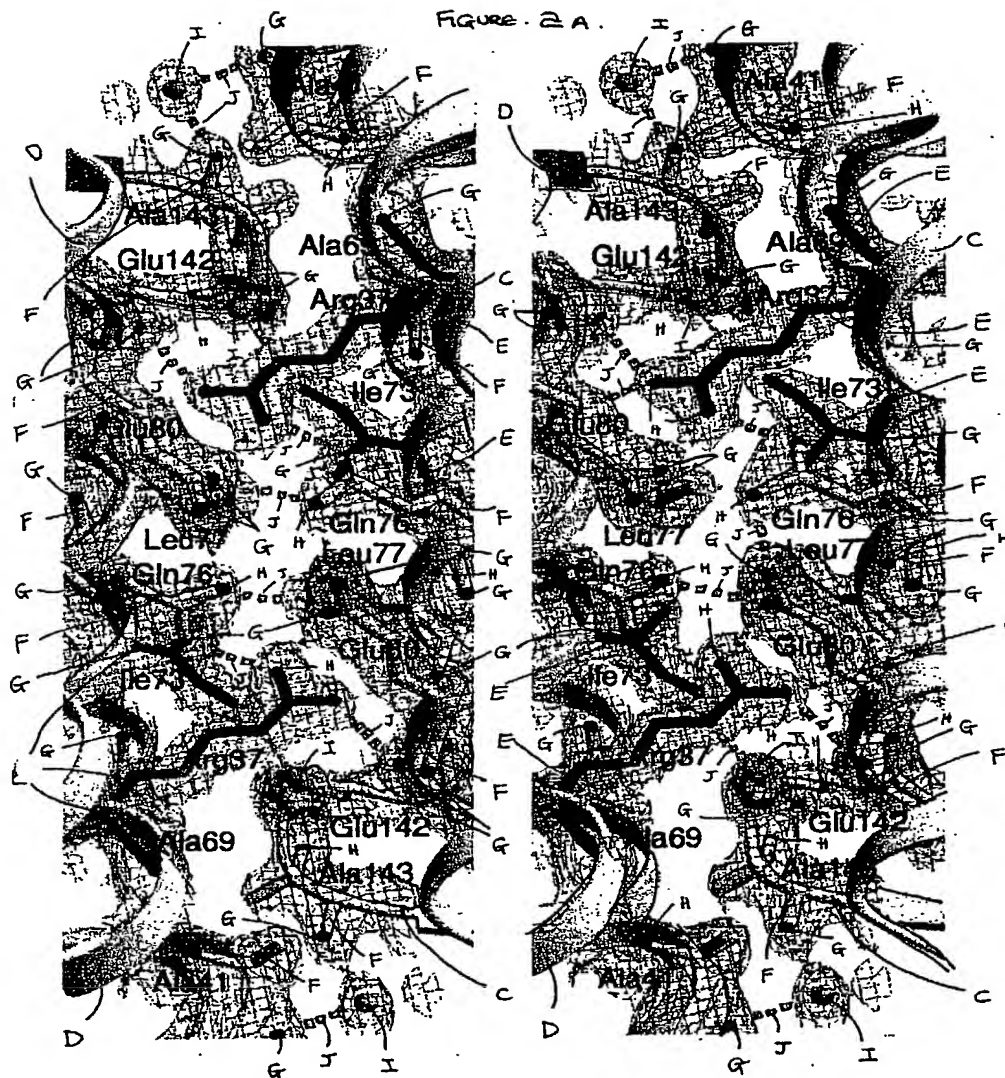
HPV 16 E2 Protein: Functional assignments



10/088245

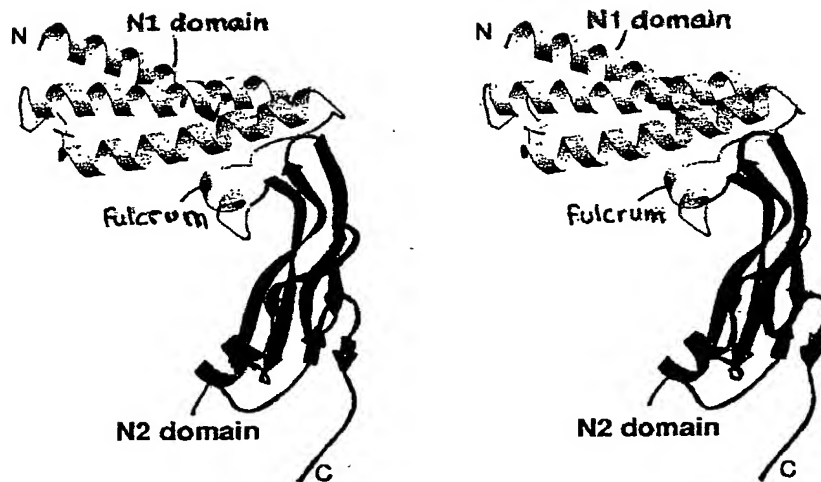
Fig. 1. B





[C = blue; monomer ribbon; D = yellow; monomer ribbon; E = dark green; side chains of Arg37 and Ile73; F = light green; side chains of other residues; G = O₂; red; H = blue; N₂; I = orange H₂O; J = dashed sticks; hydrogen bonds]

FIGURE 2B



N = N1 domain = aquamarine
 m = fulcrum = green
 L = N2 domain = pink

Fig. 2 C

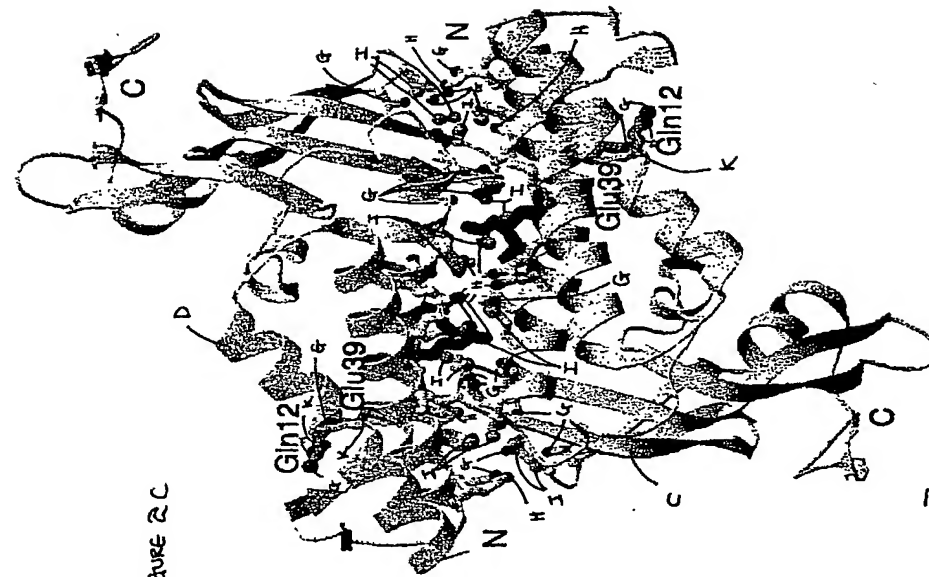
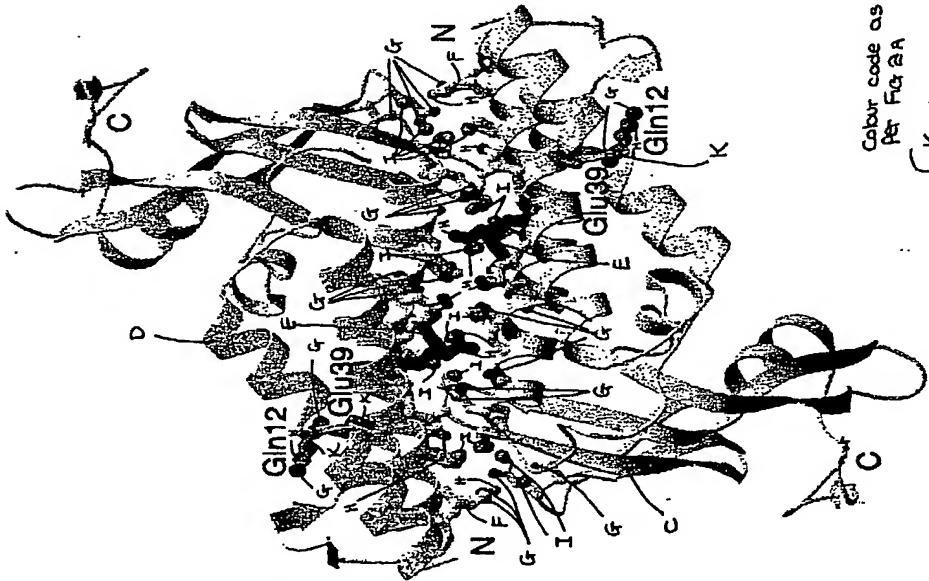


Figure 2C



Colour code as
Per Fig 2A

[K = magenta; side
chains of Gln 12 + Glu 39]

Fig 3.A.

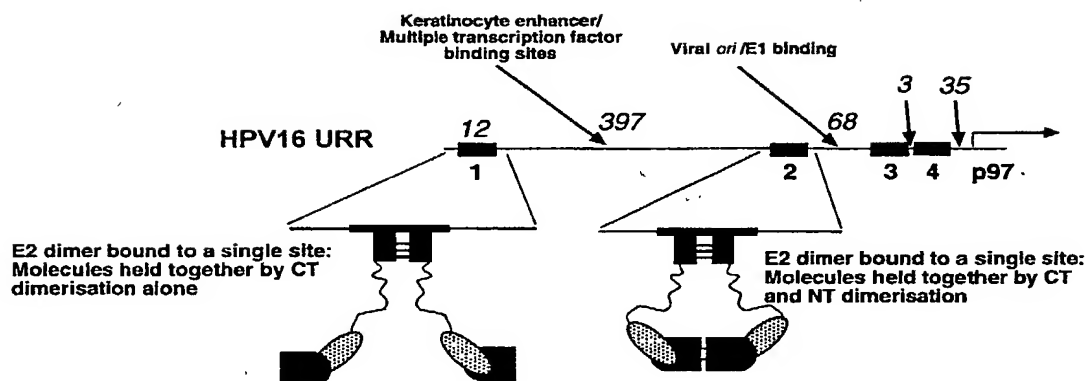


Fig. 3B

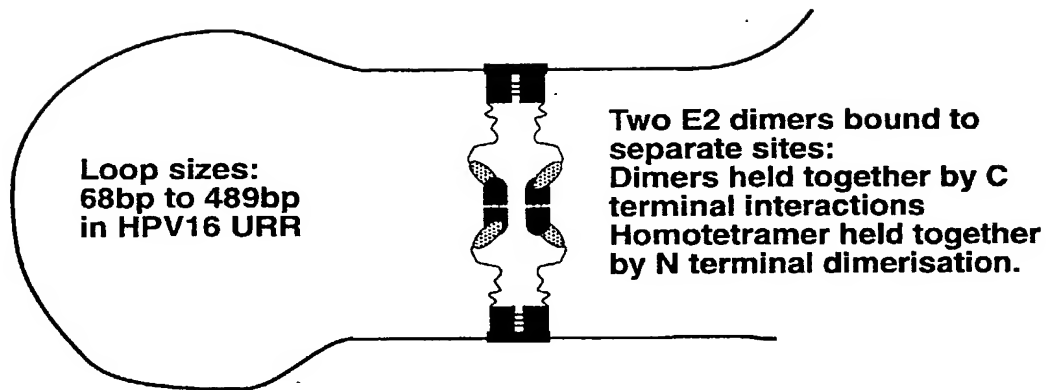


FIG. 3.C

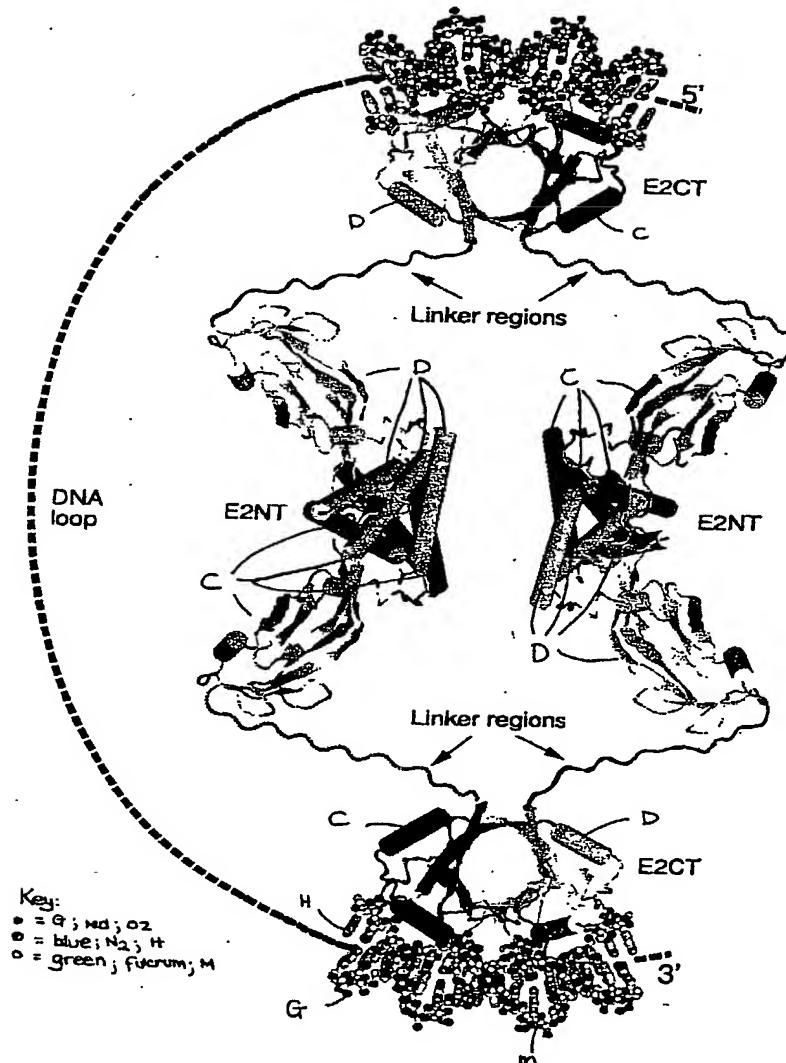


Fig. 3.D

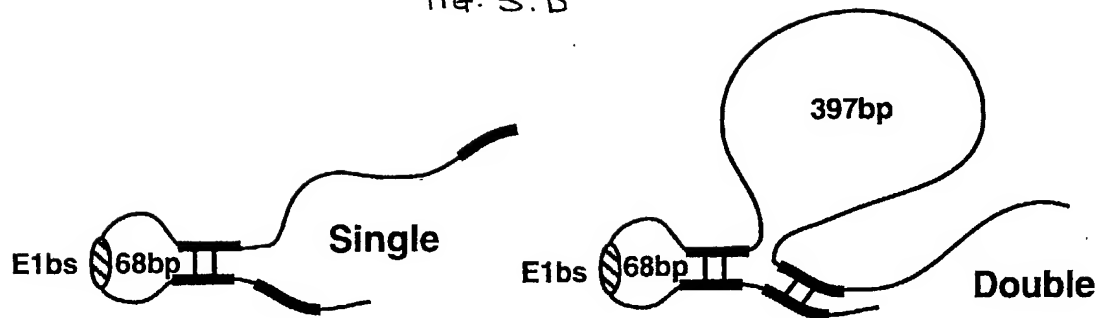


FIG. 4 A.

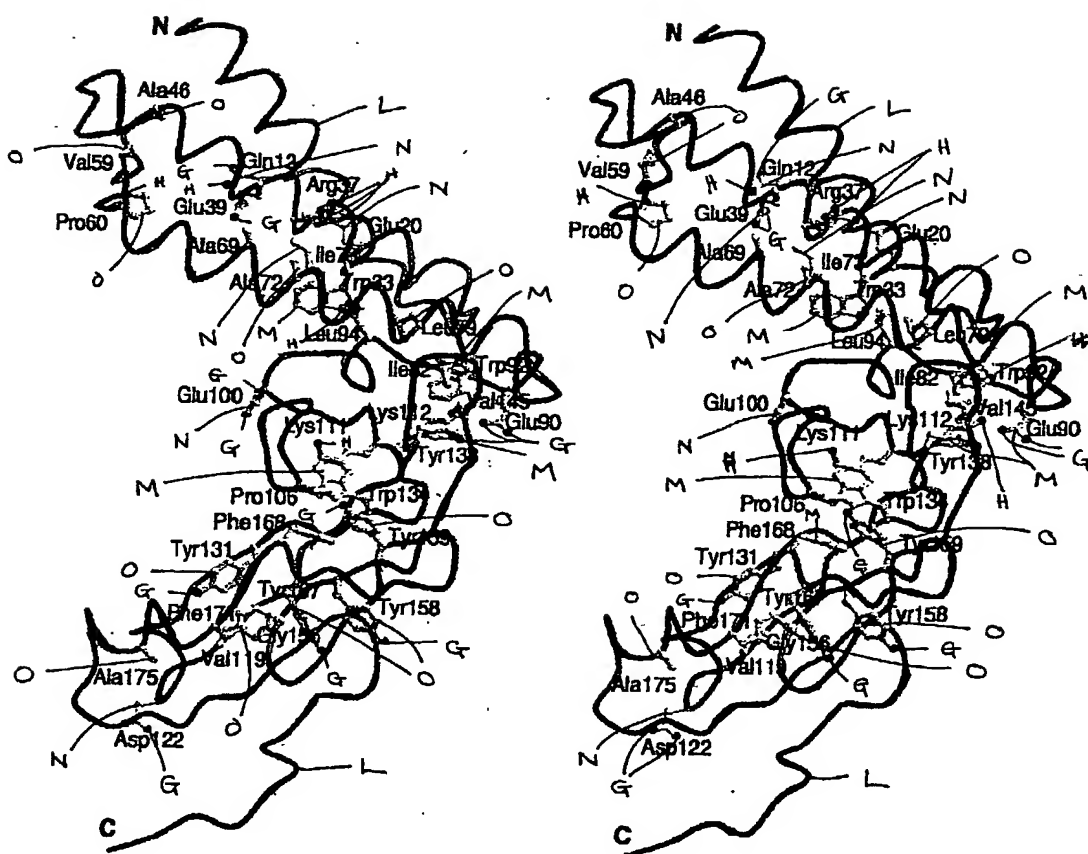


FIG. 4.B

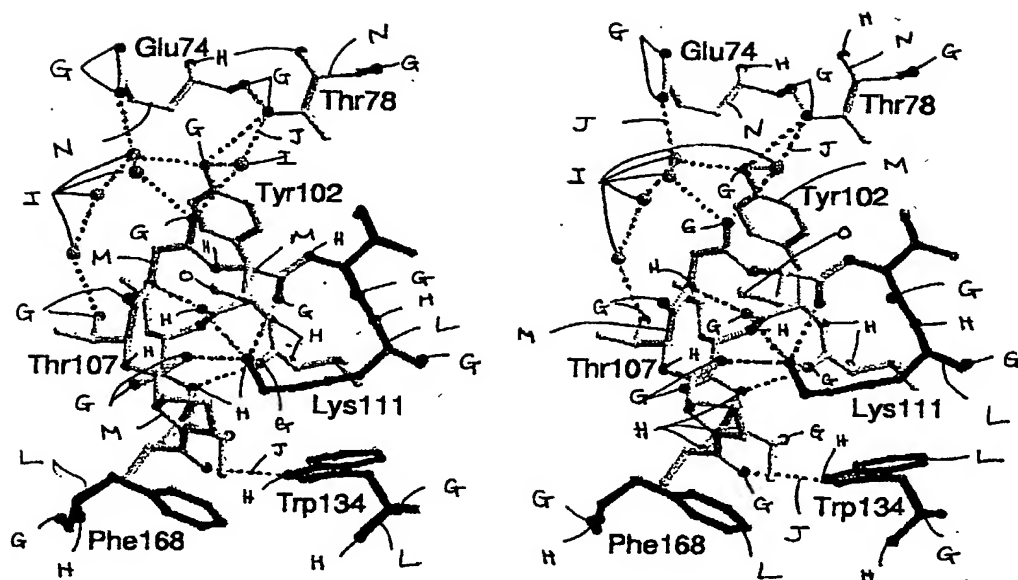


FIG. 4C

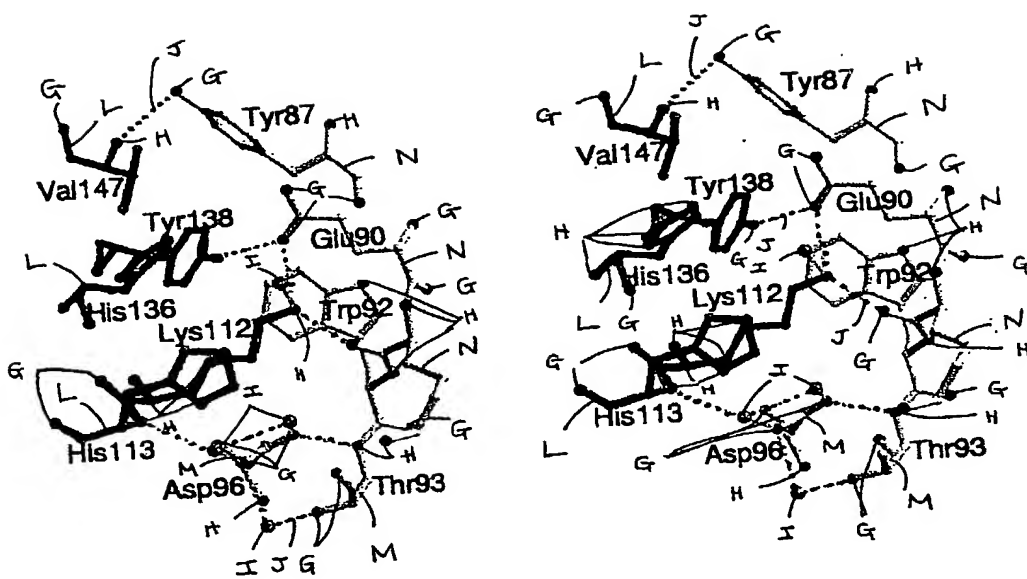
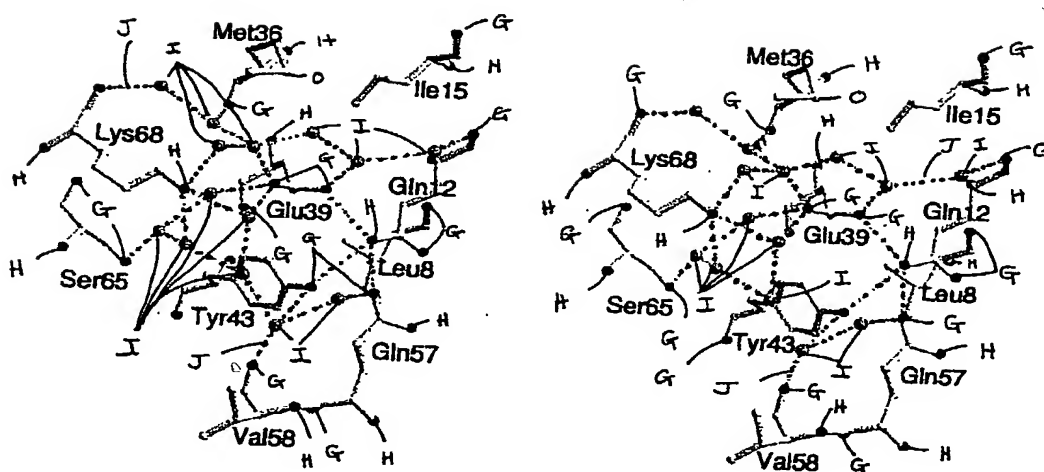


Figure 4 D.



Attorney Docket No. 9052-111

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the specification of which

☐ is attached hereto

OR

☒ was filed on **September 18, 2002** as United States Application No. or PCT International Application Number **PCT/GB00/03568** and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56, including material information that became available between the filing date of the prior application and the National or PCT International filing date of the continuation-in-part application, if applicable.

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9921938.8	Great Britain	09/17/1999	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Number	Country	MM/DD/YYYY Filed	Priority Claimed
			<input type="checkbox"/> Yes <input type="checkbox"/> No
Number	Country	MM/DD/YYYY Filed	Priority Claimed
			<input type="checkbox"/> Yes <input type="checkbox"/> No
Number	Country	MM/DD/YYYY Filed	Priority Claimed

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None	
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Application Number(s)	Filing Date (MM/DD/YYYY)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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